(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 612 846 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
16.08.2000 Bulletin 2000/33

(51) Int. Cl.[7]: **C12N 15/27**, C12P 21/02, C07K 14/53, G06F 17/50

(21) Application number: **94101207.2**

(22) Date of filing: **27.01.1994**

(54) G-CSF analog compositions and methods

G-CSF Analoge und Verfahren zu ihrer Herstellung

Analogues de G-CSF et méthodes pour les obtenir

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: **28.01.1993 US 10099**

(43) Date of publication of application:
31.08.1994 Bulletin 1994/35

(83) **Declaration under Rule 28(4) EPC (expert solution)**

(60) Divisional application:
99113571.6 / 0 974 655
99112115.3 / 0 965 638
98113221.0 / 0 890 640

(73) Proprietor: **AMGEN INC.**
Thousand Oaks, CA 91320-1789 (US)

(72) Inventor: **Osslund, Timothy**
Camarillo, California 93010 (US)

(74) Representative:
Brown, John David et al
FORRESTER & BOEHMERT
Franz-Joseph-Strasse 38
80801 München (DE)

(56) References cited:

EP-A- 0 344 796	EP-A- 0 456 200
WO-A-87/01132	WO-A-88/01775
WO-A-89/05824	WO-A-93/25687

- **DISSERTATION ABSTRACTS INTERNATIONAL B. vol. 54, no. 3 , September 1993 page 1239 T. OSSLUND ET AL 'The structure of granulocyte-colony stimulating factor'**
- **PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA vol. 90 , June 1993 , WASHINGTON US pages 5167 - 5171 C.P. HILL ET AL 'The structure of Granulocyte-colony-stimulating factor and its relationship to other growth factors'**
- **CELL STRUCTURE AND FUNCTION vol. 17, no. 1 , February 1992 pages 61 - 65 MASAHARU ISHIKAWA ET AL 'The sustitution of Cysteine 17 of recombinant human G-CSF with Alanine greatly enhanced its stability'**
- **BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS vol. 159, no. 1 , 28 February 1989 , DULUTH, MINNESOTA US pages 103 - 111 TETSURO KUGA ET AL 'Mutagenesis of human granulocyte colony stimulating factor'**
- **BIOCHEMISTRY vol. 30 , 1991 , EASTON, PA US pages 4151 - 4159 L. ABRAHMSEN ET AL 'Engineering subtilisin and its sustrates for efficient ligation of peptide bonds in aqueous solution'**
- **SCIENCE vol. 258 , 20 November 1992 , LANCASTER, PA US pages 1358 - 1362 J. PANDIT ET AL 'Three-dimensional Structure of dimeric human recombinant Macrophage Colony-Stimulating Factor'**

EP 0 612 846 B1

(Cont. next page)

- JOURNAL OF CELLULAR BIOCHEMISTRY SUPPL 0 no. 17B , 26 JANUARY-10 FEBRUARY 1993 page 78 J. E. LAYTON ET AL 'Interaction of G-CSF with its receptor : Dissociation of biological activity and Receptor binding'
- JOURNAL OF APPLIED CRYSTALLOGRAPHY vol. 20 , 1987 pages 366 - 373 M.J. COX ET AL 'Experiments with automated protein crystallization'
- POUR LA SCIENCE vol. 183 , January 1993 pages 76 - 82 A. OLSON ET AL 'Voir les Molécules biologiques'
- PROTEIN ENGINEERING 1987 , ALAN R. LISS, INC. pages 35 - 44 M. KARPLUS 'The prediction and Analysis of mutant strutures'

Description

Field of the Invention

[0001] This invention relates to granulocyte colony stimulating factor ("G-CSF") analogs.

Background

[0002] Hematopoiesis is controlled by two systems: the cells within the bone marrow microenvironment and growth factors. The growth factors, also called colony stimulating factors, stimulate committed progenitor cells to proliferate and to form colonies of differentiating blood cells. One of these factors is granulocyte colony stimulating factor, herein called G-CSF, which preferentially stimulates the growth and development of neutrophils, indicating a potential use in neutropenic states. Welte et al., PNAS-USA 82: 1526-1530 (1985); Souza et al., Science 232: 61-65 (1986) and Gabrilove, J. Seminars in Hematology 26: (2) 1-14 (1989).

[0003] In humans, endogenous G-CSF is detectable in blood plasma. Jones et al., Bailliere's Clinical Hematology 2 (1): 83-111 (1989). G-CSF is produced by fibroblasts, macrophages, T cells trophoblasts, expression product of a single copy gene comprised of four exons and five introns located on chromosome seventeen. Transcription of this locus produces a mRNA species which is differentially processed, resulting in two forms of G-CSF mRNA, one version coding for a protein of 177 amino acids, the other coding for a protein of 174 amino acids, Nagata et al., EMBO J 5: 575-581 (1986), and the form comprised of 174 amino acids has been found to have the greatest specific in vivo biological activity. G-CSF is species cross-reactive, such that when human G-CSF is administered to another mammal such as a mouse, canine or monkey, sustained neutrophil leukocytosis is elicited. Moore et al., PNAS-USA 84: 7134-7138 (1987).

[0004] Human G-CSF can be obtained and purified from a number of sources. Natural human G-CSF (nhG-CSF) can be isolated from the supernatants of cultured human tumor cell lines. The development of recombinant DNA technology, see, for instance, U.S. Patent 4,810,643 (Souza) incorporated herein by reference, has enabled the production of commercial scale quantities of G-CSF in glycosylated form as a product of eukaryotic host cell expression, and of G-CSF in non-glycosylated form as a product of prokaryotic host cell expression.

[0005] G-CSF has been found to be useful in the treatment of indications where an increase in neutrophils will provide benefits. For example, for cancer patients, G-CSF is beneficial as a means of selectively stimulating neutrophil production to compensate for hematopoietic deficits resulting from chemotherapy or radiation therapy. Other indications include treatment of various infectious diseases and related conditions, such as sepsis, which is typically caused by a metabolite of bacteria. G-CSF is also useful alone, or in combination with other compounds, such as other cytokines, for growth or expansion of cells in culture, for example, for bone marrow transplants.

[0006] Signal transduction, the way in which G-CSF effects cellular metabolism, is not currently thoroughly understood. G-CSF binds to a cell-surface receptor which apparently initiates the changes within particular progenitor cells, leading to cell differentiation.

[0007] Various altered G-CSF's have been reported. Generally, for design of drugs, certain changes are known to have certain structural effects. For example, deleting one cysteine could result in the unfolding of a molecule which is, in its unaltered state, is normally folded via a disulfide bridge. There are other known methods for adding, deleting or substituting amino acids in order to change the function of a protein.

[0008] Recombinant human G-CSF mutants have been prepared, but the method of preparation does not include overall structure/function relationship information. For example, the mutation and biochemical modification of Cys 18 has been reported. Kuga et al., Biochem. Biophy. Res. Comm 159: 103-111 (1989); Lu et al., Arch. Biochem. Biophys. 268: 81-92 (1989).

[0009] In U.S. Patent No. 4, 810, 643, entitled, "Production of Pluripotent Granulocyte Colony-Stimulating Factor" (as cited above), polypeptide analogs and peptide fragments of G-CSF are disclosed generally. Specific G-CSF analogs disclosed include those with the cysteins at positions 17, 36, 42, 64, and 74 (of the 174 amino acid species or of those having 175 amino acids, the additional amino acid being an N-terminal methionine) substituted with another amino acid, (such as serine), and G-CSF with an alanine in the first (N-terminal) position.

[0010] EP 0 335 423 entitled "Modified human G-CSF" reportedly discloses the modification of at least one amino group in a polypeptide having hG-CSF activity.

[0011] EP 0 272 703 entitled "Novel Polypeptide" reportedly discloses G-CSF derivatives having an amino acid substituted or deleted at or "in the neighborhood" of the N terminus.

[0012] EP 0 459 630, entitled "Polypeptides" reportedly discloses derivatives of naturally occurring G-CSF having at least one of the biological properties of naturally occurring G-CSF and a solution stability of at least 35% at 5 mg/ml in which the derivative has at least Cys^{17} of the native sequence replaced by a Ser^{17} residue and Asp^{27} of the native sequence replaced by a Ser^{27} residue.

[0013] EP 0 256 843 entitled "Expression of G-CSF and Muteins Thereof and Their Uses" reportedly discloses a

modified DNA sequence encoding G-CSF wherein the N-terminus is modified for enhanced expression of protein in recombinant host cells, without changing the amino acid sequence of the protein.

[0014] EP 0 243 153 entitled "Human G-CSF Protein Expression" reportedly discloses G-CSF to be modified by inactivating at least one yeast KEX2 protease processing site for increased yield in recombinant production using yeast.

[0015] Shaw, U.S. Patent No. 4,904,584, entitled "Site-Specific Homogeneous Modification of Polypeptides," reportedly discloses lysine altered proteins.

[0016] WO/9012874 reportedly discloses cysteine altered variants of proteins.

[0017] Australian patent application Document No. AU-A-10948/92, entitled, "Improved Activation of Recombinant Proteins" reportedly discloses the addition of amino acids to either terminus of a G-CSF molecule for the purpose of aiding in the folding of the molecule after prokaryotic expression.

[0018] Australian patent application Document No. AU-A-76380/91, entitled, "Muteins of the Granulocyte Colony Stimulating Factor (G-CSF)" reportedly discloses muteins of the granulocyte stimulating factor G-CSF in the sequence Leu-Gly-His-Ser-Leu-Gly-Ile at position 50-56 of G-CSF with 174 amino acids, and position 53 to 59 of the G-CSF with 177 amino acids, or/and at least one of the four histadine residues at positions 43, 79, 156 and 170 of the mature G-CSF with 174 amino acids or at positions 46, 82, 159, or 173 of the mature G-CSF with 177 amino acids.

[0019] GB 2 213 821, entitled "Synthetic Human Granulocyte Colony Stimulating Factor Gene" reportedly discloses a synthetic G-CSF-encoding nucleic acid sequence incorporating restriction sites to facilitate the cassette mutagenesis of selected regions, and flanking restriction sites to facilitate the incorporation of the gene into a desired expression system.

[0020] G-CSF has reportedly been crystallized to some extent, e.g., EP 344 796, and the overall structure of G-CSF has been surmised, but only on a gross level. Bazan, Immunology Today 11: 350-354 (1990); Parry et al., J. Molecular Recognition 8: 107-110 (1988). To date, there have been no reports of the overall structure of G-CSF, and no systematic studies of the relationship of the overall structure and function of the molecule, studies which are essential to the systematic design of G-CSF analogs. Accordingly, there exists a need for a method of this systematic design of G-CSF analogs, and the resultant compositions.

Summary of the Invention

[0021] The three dimensional structure of G-CSF has now been determined to the atomic level. From this three-dimensional structure, one can now forecast with substantial certainty how changes in the composition of a G-CSF molecule may result in structural changes. These structural characteristics may be correlated with biological activity to design and produce G-CSF analogs.

[0022] Although others had speculated regarding the three dimensional structure of G-CSF, Bazan, Immunology Today 11: 350-354 (1990); Parry et al., J. Molecular Recognition 8: 107-110 (1988), these speculations were of no help to those wishing to prepare G-CSF analogs either because the surmised structure was incorrect (Parry et al., supra) and/or because the surmised structure provided no detail correlating the constituent moieties with structure. The present determination of the three-dimensional structure to the atomic level is by far the most complete analysis to date, and provides important information to those wishing to design and prepare G-CSF analogs. For example, from the present three dimensional structural analysis, precise areas of hydrophobicity and hydrophilicity have been determined.

[0023] Relative hydrophobicity is important because it directly relates to the stability of the molecule. Generally, biological molecules, found in aqueous environments, are externally hydrophilic and internally hydrophobic; in accordance with the second law of thermodynamics provides, this is the lowest energy state and provides for stability. Although one could have speculated that G-CSF's internal core would be hydrophobic, and the outer areas would be hydrophilic, one would have had no way of knowing specific hydrophobic or hydrophilic areas. With the presently provided knowledge of areas of hydrophobicity/philicity, one may forecast with substantial certainty which changes to the G-CSF molecule will affect the overall structure of the molecule.

[0024] As a general rule, one may use knowledge of the geography of the hydrophobic and hydrophilic regions to design analogs in which the overall G-CSF structure is not changed, but change does affect biological activity ("biological activity" being used here in its broadest sense to denote function). One may correlate biological activity to structure. If the structure is not changed, and the mutation has no effect on biological activity, then the mutation has no biological function. If, however, the structure is not changed and the mutation does affect biological activity, then the residue (or atom) is essential to at least one biological function. Some of the present working examples were designed to provide no change in overall structure, yet have a change in biological function.

[0025] Based on the correlation of structure to biological activity, the present invention relates to G-CSF analogs. These analogs are molecules which have more, fewer, different or modified amino acid residues from the G-CSF amino acid sequence. The modifications may be by addition, substitution, or deletion of one or more amino acid residues. The modification may include the addition or substitution of analogs of the amino acids themselves, such as peptidomimetics or amino acids with altered moieties such as altered side groups. The G-CSF used as a basis for comparison may

be of human, animal or recombinant nucleic acid-technology origin (although the working examples disclosed herein are based on the recombinant production of the 174 amino acid species of human G-CSF, having an extra N-terminus methionyl residue). The analogs may possess functions different from natural human G-CSF molecule, or may exhibit the same functions, or varying degrees of the same functions. For example, the analogs may be designed to have a higher or lower biological activity, have a longer shelf-life or a decrease in stability, be easier to formulate, or more difficult to combine with other ingredients. The analogs may have no hematopoietic activity, and may therefore be useful as an antagonist against G-CSF effect (as, for example, in the overproduction of G-CSF). From time to time herein the present analogs are referred to as proteins or peptides for convenience, but contemplated herein are other types of molecules, such as peptidomimetics or chemically modified peptides.

[0026] In another aspect, the present disclosure relates to related compositions containing a G-CSF analog as an active ingredient. The term, "related composition," as used herein, is meant to denote a composition which may be obtained once the identity of the G-CSF analog is ascertained (such as a G-CSF analog labeled with a detectable label, related receptor or pharmaceutical composition). Also considered a related composition are chemically modified versions of the G-CSF analog, such as those having attached at least one polyethylene glycol molecule.

[0027] For example, one may prepare a G-CSF analog to which a detectable label is attached, such as a fluorescent, chemiluminescent or radioactive molecule.

[0028] Another example is a pharmaceutical composition which may be formulated by known techniques using known materials, see, e.g., Remington's Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, Pennsylvania 18042) pages 1435-1712, which are herein incorporated by reference. Generally, the formulation will depend on a variety of factors such as administration, stability, production concerns and other factors. The G-CSF analog may be administered by injection or by pulmonary administration via inhalation. Enteric dosage forms may also be available for the present G-CSF analog compositions, and therefore oral administration may be effective. G-CSF analogs may be inserted into liposomes or other microcarriers for delivery, and may be formulated in gels or other compositions for sustained release. Although preferred compositions will vary depending on the use to which the composition will be put, generally, for G-CSF analogs having at least one of the biological activities of natural G-CSF, preferred pharmaceutical compositions are those prepared for subcutaneous injection or for pulmonary administration via inhalation, although the particular formulations for each type of administration will depend on the characteristics of the analog.

[0029] Another example of related composition is a receptor for the present analog. As used herein, the term "receptor" indicates a moiety which selectively binds to the present analog molecule. For example, antibodies, or fragments thereof, or "recombinant antibodies" (see Huse et al., Science 246:1275 (1989)) may be used as receptors. Selective binding does not mean only specific binding (although binding-specific receptors are encompassed herein), but rather that the binding is not a random event. Receptors may be on the cell surface or intra- or extra-cellular, and may act to effectuate, inhibit or localize the biological activity of the present analogs. Receptor binding may also be a triggering mechanism for a cascade of activity indirectly related to the analog itself. Also contemplated herein are nucleic acids, vectors containing such nucleic acids and host cells containing such nucleic acids which encode such receptors.

[0030] Another example of a related composition is a G-CSF analog with a chemical moiety attached. Generally, chemical modification may alter biological activity or antigenicity of a protein, or may alter other characteristics, and these factors will be taken into account by a skilled practitioner. As noted above, one example of such chemical moiety is polyethylene glycol. Modification may include the addition of one or more hydrophilic or hydrophobic polymer molecules, fatty acid molecules, or polysaccharide molecules. Examples of chemical modifiers include polyethylene glycol, alkIpolyethylene glycols, DI-poly(amino acids), polyvinylpyrrolidone, polyvinyl alcohol, pyran copolymer, acetic acid/acylation, proprionic acid, palmitic acid, stearic acid, dextran, carboxymethyl cellulose, pullulan, or agarose. See, Francis, *Focus on Growth Factors* 3: 4-10 (May 1992) (published by Mediscript, Mountview Court, Friern Barnet Lane, London N20 OLD, UK). Also, chemical modification may include an additional protein or portion thereof, use of a cytotoxic agent, or an antibody. The chemical modification may also include lecithin.

[0031] In another aspect, the present disclosure relates to nucleic acids encoding such analogs. The nucleic acids may be DNAs or RNAs or derivatives thereof, and will typically be cloned and expressed on a vector, such as a phage or plasmid containing appropriate regulatory sequences. The nucleic acids may be labeled (such as using a radioactive, chemiluminescent, or fluorescent label) for diagnostic or prognostic purposes, for example. The nucleic acid sequence may be optimized for expression, such as including codons preferred for bacterial expression. The nucleic acid and its complementary strand, and modifications thereof which do not prevent encoooding of the desired analog are here contemplated.

[0032] In another aspect, the present disclosure relates to host cells containing the above nucleic acids encoding the present analogs. Host cells may be eukaryotic or prokaryotic, and expression systems may include extra steps relating to the attachment (or prevention) of sugar groups (glycosylation), proper folding of the molecule, the addition or deletion of leader sequences or other factors incident to recombinant expression.

[0033] In another aspect the present disclosure relates to antisense nucleic acids which act to prevent or modify the

type or amount of expression of such nucleic acid sequences. These may be prepared by known methods.

[0034] In another aspect of the present disclosure, the nucleic acids encoding a present analog may be used for gene therapy purposes, for example, by placing a vector containing the analog-encoding sequence into a recipient so the nucleic acid itself is expressed inside the recipient who is in need of the analog composition. The vector may first be placed in a carrier, such as a cell, and then the carrier placed into the recipient. Such expression may be localized or systemic. Other carriers include non-naturally occurring carriers, such as liposomes or other microcarriers or particles, which may act to mediate gene transfer into a recipient.

[0035] The present disclosure also provides for computer programs for the expression (such as visual display) of the G-CSF or analog three dimensional structure, and further, a computer program which expresses the identity of each constituent of a G-CSF molecule and the precise location within the overall structure of that constituent, down to the atomic level. Set forth below is one example of such program. There are many currently available computer programs for the expression of the three dimensional structure of a molecule. Generally, these programs provide for inputting of the coordinates for the three dimensional structure of a molecule (i.e., for example, a numerical assignment for each atom of a G-CSF molecule along an x, y, and z axis), means to express (such as visually display) such coordinates, means to alter such coordinates and means to express an image of a molecule having such altered coordinates. One may program crystallographic information, i.e., the coordinates of the location of the atoms of a G-CSF molecule in three dimension space, wherein such coordinates have been obtained from crystallographic analysis of said G-CSF molecule, into such programs to generate a computer program for the expression (such as visual display) of the G-CSF three dimensional structure. Also provided, therefore, is a computer program for the expression of G-CSF analog three dimensional structure. Preferred is the computer program Insight II, version 4, available from Biosym, San Diego, California, with the coordinates as set forth in FIGURE 5 input. Preferred expression means is on a Silicon Graphics 320 VGX computer, with Crystal Eyes glasses (also available from Silicon Graphics), which allows one to view the G-CSF molecule or its analog stereoscopically. Alternatively, the present G-CSF crystallographic coordinates and diffraction data are also deposited in the Protein Data Bank, Chemistry Department, Brookhaven National Laboratory, Upton, New York 119723, USA. One may use these data in preparing a different computer program for expression of the three dimensional structure of a G-CSF molecule or analog thereof. Therefore, another aspect of the present invention is a computer program for the expression of the three dimensional structure of a G-CSF molecule. Also provided is said computer program for visual display of the three dimensional structure of a G-CSF molecule; and further, said program having means for altering such visual display. Apparatus useful for expression of such computer program, particularly for the visual display of the computer image of said three dimensional structure of a G-CSF molecule or analog thereof is also therefore here provided, as well as means for preparing said computer program and apparatus.

[0036] The computer program is useful for preparation of G-CSF analogs because one may select specific sites on the G-CSF molecule for alteration and readily ascertain the effect the alteration will have on the overall structure of the G-CSF molecule. Selection of said site for alteration will depend on the desired biological characteristic of the G-CSF analog. If one were to randomly change said G-CSF molecule (r-met-hu-G-CSF) there would be 175^{20} possible substitutions, and even more analogs having multiple changes, additions or deletions. By viewing the three dimensional structure wherein said structure is correlated with the composition of the molecule, the selection for sites of alteration is no longer a random event, but sites for alteration may be determined rationally.

[0037] As set forth above, identity of the three dimensional structure of G-CSF, including the placement of each constituent down to the atomic level has now yielded information regarding which moieties are necessary to maintain the overall structure of the G-CSF molecule. One may therefore select whether to maintain the overall structure of the G-CSF molecule when preparing a G-CSF analog of the present invention, or whether (and how) to change the overall structure of the G-CSF molecule when preparing a G-CSF analog of the present invention. Optionally, once one has prepared such analog, one may test such analog for a desired characteristic.

[0038] One may, for example, seek to maintain the overall structure possessed by a non-altered natural or recombinant G-CSF molecule. The overall structure is presented in Figures 2, 3, and 4, and is described in more detail below. Maintenance of the overall structure may ensure receptor binding, a necessary characteristic for an analog possessing the hematopoietic capabilities of natural G-CSF (if no receptor binding, signal transduction does not result from the presence of the analog). It is contemplated that one class of G-CSF analogs will possess the three dimensional core structure of a natural or recombinant (non-altered) G-CSF molecule, yet possess different characteristics, such as an increased ability to selectively stimulate neutrophils. Another class of G-CSF analogs are those with a different overall structure which diminishes the ability of a G-CSF analog molecule to bind to a G-CSF receptor, and possesses a diminished ability to selectively stimulate neutrophils as compared to non-altered natural or recombinant G-CSF.

[0039] For example, it is now known which moieties within the internal regions of the G-CSF molecule are hydrophobic, and, correspondingly, which moieties on the external portion of the G-CSF molecule are hydrophilic. Without knowledge of the overall three dimensional structure, preferably to the atomic level as provided herein, one could not forecast which alterations within this hydrophobic internal area would result in a change in the overall structural conformation of the molecule. An overall structural change could result in a functional change, such as lack of receptor bind-

ing, for example, and therefore, diminishment of biological activity as found in non-altered G-CSF. Another class of G-CSF analogs is therefore G-CSF analogs which possess the same hydrophobicity as (non-altered) natural or recombinant G-CSF. More particularly, another class of G-CSF analogs possesses the same hydrophobic moieties within the four helical bundle of its internal core as those hydrophobic moieties possessed by (non-altered) natural or recombinant G-CSF yet have a composition different from said non-altered natural or recombinant G-CSF.

[0040] Another example relates to external loops which are structures which connect the internal core (helices) of the G-CSF molecule. From the three dimensional structure -- including information regarding the spatial location of the amino acid residues -- one may forecast that certain changes in certain loops will not result in overall conformational changes. Therefore, another class of G-CSF analogs provided herein is that having an altered external loop but possessing the same overall structure as (non-altered) natural or recombinant G-CSF. More particularly, another class of G-CSF analogs provided herein are those having an altered external loop, said loop being selected from the loop present between helices A and B; between helices B and C; between helices C and D; between helices D and A, as those loops and helices are identified herein. More particularly, said loops, preferably the AB loop and/or the CD loop are altered to increase the half life of the molecule by stabilizing said loops. Such stabilization may be by connecting all or a portion of said loop(s) to a portion of an alpha helical bundle found in the core of a G-CSF (or analog) molecule. Such connection may be via beta sheet, salt bridge, disulfide bonds, hydrophobic interaction or other connecting means available to those skilled in the art, wherein such connecting means serves to stabilize said external loop or loops. For example, one may stabilize the AB or CD loops by connecting the AB loop to one of the helices within the internal region of the molecule.

[0041] The N-terminus also may be altered without change in the overall structure of a G-CSF molecule, because the N-terminus does not effect structural stability of the internal helices, and, although the external loops are preferred for modification, the same general statements apply to the N-terminus.

[0042] Additionally, such external loops may be the site(s) for chemical modification because in (non-altered) natural or recombinant G-CSF such loops are relatively flexible and tend not to interfere with receptor binding. Thus, there would be additional room for a chemical moiety to be directly attached (or indirectly attached via another chemical moiety which serves as a chemical connecting means). The chemical moiety may be selected from a variety of moieties available for modification of one or more function of a G-CSF molecule. For example, an external loop may provide sites for the addition of one or more polymer which serves to increase serum half-life, such as a polyethylene glycol molecule. Such polyethylene glycol molecule(s) may be added wherein said loop is altered to include additional lysines which have reactive side groups to which polyethylene glycol moieties are capable of attaching. Other classes of chemical moieties may also be attached to one or more external loops, including but not limited to other biologically active molecules, such as receptors, other therapeutic proteins (such as other hematopoietic factors which would engender a hybrid molecule), or cytotoxic agents (such as diphtheria toxin). This list is of course not complete; one skilled in the art possessed of the desired chemical moiety will have the means to effect attachment of said desired moiety to the desired external loop. Therefore, another class of the present G-CSF analogs includes those with at least one alteration in an external loop wherein said alteration provides for the addition of a chemical moiety such as at least one polyethylene glycol molecule.

[0043] Deletions, such as deletions of sites recognized by proteins for degradation of the molecule, may also be effectual in the external loops. This provides alternative means for increasing half-life of a molecule otherwise having the G-CSF receptor binding and signal transduction capabilities (i.e., the ability to selectively stimulate the maturation of neutrophils). Therefore, another class of the present G-CSF analogs includes those with at least one alteration in an external loop wherein said alteration decreases the turnover of said analog by proteases. Preferred loops for such alterations are the AB loop and the CD loop. One may prepare an abbreviated G-CSF molecule by deleting a portion of the amino acid residues found in the external loops (identified in more detail below), said abbreviated G-CSF molecule may have additional advantages in preparation or in biological function.

[0044] Another example relates to the relative charges between amino acid residues which are in proximity to each other. As noted above, the G-CSF molecule contains a relatively tightly packed four helical bundle. Some of the faces on the helices face other helices. At the point (such as a residue) where a helix faces another helix, the two amino acid moieties which face each other may have the same charge, and thus tend to repel each other, which lends instability to the overall molecule. This may be eliminated by changing the charge (to an opposite charge or a neutral charge) of one or both of the amino acid moieties so that there is no repelling. Therefore, another class of G-CSF analogs includes those G-CSF analogs having been altered to modify instability due to surface interactions, such as electron charge location.

[0045] Th present invention relates to methods for designing G-CSF analogs and related compositions and the products of those methods. The end products of the methods may be the G-CSF analogs as defined above or related compositions. For instance, the examples disclosed herein demonstrate (a) the effects of changes in the constitu nts (i.e., chemical moieties) of the G-CSF molecule on the G-CSF structure and (b) the effects of changes in structure on biological function. Essentially, therefore, an aspect of the present invention is a method for preparing a G-CSF analog

comprising the steps of:

(a) viewing at an amino acid or atomic level information conveying the three dimensional structure of a G-CSF molecule as set forth in Figure 5 wherein the chemical moieties, such as each amino acid residue or each atom of each amino acid residue, of the G-CSF molecule are correlated with said structure;
(b) selecting from said information a site on a G-CSF molecule for alteration;
(c) preparing a G-CSF analog molecule having such alteration; and
(d) optionally, testing such G-CSF analog molecule for a desired characteristic.

[0046] One may use the here provided computer programs for a computer-based method for preparing a G-CSF analog. Another aspect of the present invention is therefore a method for preparing a G-CSF analog according to the method of the preceeding paragraph based on the use of a computer comprising the steps of:

(a) providing computer expression of the three dimensional structure of a G-CSF molecule wherein the chemical moieties, such as each amino acid residue or each atom of each amino acid residue, of the G-CSF molecule are correlated with said structure;
(b) selecting from said computer expression a site on a G-CSF molecule for alteration;
(c) preparing a G-CSF molecule having such alteration; and
(d) optionally, testing such G-CSF molecule for a desired characteristic.

[0047] More specifically, the present invention provides a method for preparing a G-CSF analog comprising the steps of:

(a) viewing at the amino acid or atomic level the three dimensional structure of a G-CSF molecule as set forth in Figure 5 via a computer, said computer programmed (i) to express the coordinates of a G-CSF molecule in three dimensional space, and (ii) to allow for entry of information for alteration of said G-CSF expression and viewing thereof;
(b) selecting a site on said visual image of said G-CSF molecule for alteration;
(c) entering information for said alteration on said computer;
(d) viewing a three dimensional structure of said altered G-CSF molecule via said computer;
(e) optionally repeating steps (a)-(e);
(f) preparing a G-CSF analog with said alteration; and
(g) optionally testing said G-CSF analog for a desired characteristic.

[0048] In another aspect, the present disclosure relates to methods of using the present G-CSF analogs and related compositions and methods for the treatment or protection of mammals, either alone or in combination with other hematopoietic factors or drugs in the treatment of hematopoietic disorders. It is contemplated that one aspect of designing G-CSF analogs will be the goal of enhancing or modifying the characteristics non-modified G-CSF is known to have.

[0049] For example, the analogs may possess enhanced or modified activities, so, where G-CSF is useful in the treatment of (for example) neutropenia, the present compositions and methods may also be of such use.

[0050] Another example is the modification of G-CSF for the purpose of interacting more effectively when used in combination with other factors particularly in the treatment of hematopoietic disorders. One example of such combination use is to use an early-acting hematopoietic factor (i.e., a factor which acts earlier in the hematopoiesis cascade on relatively undifferentiated cells) and either simultaneously or in seriatim use of a later-acting hematopoietic factor, such as G-CSF or analog thereof (as G-CSF acts on the CFU-GM lineage in the selective stimulation of neutrophils). The methods and compositions may be useful in therapy involving such combinations or "cocktails" of hematopoietic factors.

[0051] The compositions and methods may also be useful in the treatment of leukopenia, mylogenous leukemia, severe chronic neutropenia, aplastic anemia, glycogen storage disease, mucosistitis, and other bone marrow failure states. The compositions and methods may also be useful in the treatment of hematopoietic deficits arising from chemotherapy or from radiation therapy. The success of bone marrow transplantation, or the use of peripheral blood progenitor cells for transplantation, for example, may be enhanced by application of the present compositions (proteins or nucleic acids for gene therapy) and methods. The compositions and methods may also be useful in the treatment of infectious diseases, such in the context of wound healing, burn treatment, bacteremia, septicemia, fungal infections, endocarditis, osteopyelitis, infection related to abdominal trauma, infections not responding to antibiotics, pneumonia and the treatment of bacterial inflammation may also benefit from the application of the compositions and methods. In addition, the compositions and methods may be useful in the treatment of leukemia based upon a reported ability to differentiate leukemic cells. Welte et al., PNAS-USA 82: 1526-1530 (1985). Other applications include the treatment of individuals with tumors, using the compositions and methods, optionally in the presence of receptors (such as antibod-

ies) which bind to the tumor cells. For review articles on therapeutic applications, see Lieshhke and Burgess, N.Engl.J.Med. 327: 28-34 and 99-106 (1992) both of which are herein incorporated by reference.

[0052] The compositions and methods may also be useful to act as intermediaries in the production of other moieties; for example, G-CSF has been reported to influence the production of other hematopoietic factors and this function (if ascertained) may be enhanced or modified via the present compositions and/or methods.

[0053] The compositions related to the present G-CSF analogs, such as receptors, may be useful to act as an antagonist which prevents the activity of G-CSF or an analog. One may obtain a composition with some or all of the activity of non-altered G-CSF or a G-CSF analog, and add one or more chemical moieties to alter one or more properties of such G-CSF or analog. With knowledge of the three dimensional conformation, one may forecast the best geographic location for such chemical modification to achieve the desired effect.

[0054] General objectives in chemical modification may include improved half-life (such as reduced renal, immunological or cellular clearance), altered bioactivity (such as altered enzymatic properties, dissociated bioactivities or activity in organic solvents), reduced toxicity (such as concealing toxic epitopes, compartmentalization, and selective biodistribution), altered immunoreactivity (reduced immunogenicity, reduced antigenicity or adjuvant action), or altered physical properties (such as increased solubility, improved thermal stability, improved mechanical stability, or conformational stabilization). See Francis, *Focus on Growth Factors* 3: 4-10 (May 1992) (published by Mediscript, Mountview Court, Friern Barnet Lane, London N20 OLD, UK).

[0055] The examples below are illustrative of the present invention and are not intended as a limitation. It is understood that variations and modifications will occur to those skilled in the art, and it is intended that the appended claims cover all such equivalent variations which come within the scope of the invention as claimed.

Detailed Description of the Drawings

[0056]

FIGURE 1 is an illustration of the amino acid sequence of the 174 amino acid species of G-CSF with an additional N-terminal methionine (Seq. ID No.: 1) (Seq. ID No.: 2).

FIGURE 2 is an topology diagram of the crystalline structure of G-CSF, as well as hGH, pGH, GM-CSF, INF-B, IL-2, and IL-4. These illustrations are based on inspection of cited references. The length of secondary structural elements are drawn in proportion to the number of residues. A, B, C, and D helices are labeled according to the scheme used herein for G-CSF. For INF-β, the original labeling of helices is indicated in parentheses. FIGURE 3 is an "ribbon diagram" of the three dimensional structure of G-CSF. Helix A is amino acid residues 11-39 (numbered according to Figure 1, above), helix B is amino acid residues 72-91, helix C is amino acid residues 100-123, and helix D is amino acid residues 143-173. The relatively short 3^{10} helix is at amino acid residues 45-48, and the alpha helix is at amino acid residues 48-53. Residues 93-95 form almost one turn of a left handed helix.

FIGURE 4 is a "barrel diagram" of the three dimensional structure of G-CSF. Shown in various shades of gray are the overall cylinders and their orientations for the three dimensional structure of G-CSF. The numbers indicate amino acid residue position according to FIGURE 1 above.

FIGURE 5 is a list of the coordinates used to generate a computer-aided visual image of the three-dimensional structure of G-CSF. The coordinates are set forth below. The columns correspond to separate field:

(i) Field 1 (from the left hand side) is the atom,
(ii) Field 2 is the assigned atom number,
(iii) Field 3 is the atom name (according to the periodic table standard nomenclature, with CB being carbon atom Beta, CG is Carbon atom Gamma, etc.);
(iv) Field 4 is the residue type (according to three letter nomenclature for amino acids as found in, e.g., Stryer, Biochemistry, 3d Ed., W.H. Freeman and Company, N.Y. 1988, inside back cover);
(v) Fields 5-7 are the x-axis, y-axis and z-axis positions of the atom;
(vi) Field 8 (often a "1.00") designates occupancy at that position;
(vii) Field 9 designates the B-factor;
(viii) Field 10 designates the molecule designation. Three molecules (designated a, b, and c) of G-CSF crystallized together as a unit. The designation a, b, or c indicates which coordinates are from which molecule. The number after the letter (1, 2, or 3) indicates the assigned amino acid residue position, with molecule A having assigned positions 10-175, molecule B having assigned positions 210-375, and molecule C having assigned positions 410-575. These positions were so designated so that there would be no overlap among the three molecules which crystallized together. (The "W" designation indicates water).

FIGURE 6 is a schematic representation of the strategy involved in refining the crystallization matrix for parameters

involved in crystallization. The crystallization matrix corresponds to the final concentration of the components (salts, buffers and precipitants) of the crystallization solutions in the wells of a 24 well tissue culture plate. These concentrations are produced by pipetting the appropriate volume of stock solutions into the wells of the microtiter plate. To design the matrix, the crystallographer decides on an upper and lower concentration of the component. These upper and lower concentrations can be pipetted along either the rows (e.g., A1-A6, B1-B6, C1-C6 or D1-D6) or along the entire tray (A1-D6). The former method is useful for checking reproducibility of crystal growth of a single component along a limited number of wells, whereas the later method is more useful in initial screening. The results of several stages of refinement of the crystallization matrix are illustrated by a representation of three plates. The increase in shading in the wells indicates a positive crystallization result which, in the final stages, would be X-ray quality crystals but in the initial stages could be oil droplets, granular precipitates or small crystals approximately less than 0.05 mm in size. Part A represents an initial screen of one parameter in which the range of concentration between the first well (A1) and last well (D6) is large and the concentration increase between wells is calculated as ((concentration A1)-(concentration D6))/23). Part B represents that in later stages of the crystallization matrix refinement of the concentration spread between A1 and D6 would be reduced which would result in more crystals formed per plate. Part C indicates a final stage of matrix refinement in which quality crystals are found in most wells of the plate.

Detailed Description of the Invention

[0057] The present invention grows out of the discovery of the three dimensional structure of G-CSF. This three dimensional structure has been expressed via computer program for stereoscopic viewing. By viewing this stereoscopically, structure-function relationships identified and G-CSF analogs have been designed and made.

The Overall Three Dimensional Structure of G-CSF

[0058] The G-CSF used to ascertain the structure was a non-glycosylated 174 amino acid species having an extra N-terminal methionine residue incident to bacterial expression. The DNA and amino acid sequence of this G-CSF are illustrated in FIGURE 1.

[0059] Overall, the three dimensional structure of G-CSF is predominantly helical, with 103 of the 175 residues forming a 4-alpha-helical bundle. The only other secondary structure is found in the loop between the first two long helices where a 4 residue 3^{10} helix is immediately followed by a 6 residue alpha helix. As shown in FIGURE 2, the overall structure has been compared with the structure reported for other proteins: growth hormone (Abdel-Meguid et al., PNAS-USA 84: 6434 (1987) and Vos et al., Science 255: 305-312 (1992)), granulocyte macrophage colony stimulating factor (Diederichs et al., Science 254: 1779-1782 (1991), interferon-β (Senda et al., EMBO J. 11: 3193-3201 (1992)), interleukin-2 (McKay Science 257: 1673-1677 (1992)) and interleukin-4 (Powers et al., Science 256: 1673-1677 (1992), and Smith et al., J. Mol. Biol. 224: 899-904 (1992)). Structural similarity among these growth factors occurs despite the absence of similarity in their amino acid sequences.

[0060] Presently, the structural information was correlation of G-CSF biochemistry, and this can be summarized as follows (with sequence position 1 being at the N-terminus):

Sequence Position	Description of Structure	Analysis
1-10	Extended chain	Deletion causes no loss of biological activity
Cys 18	Partially buried	Reactive with DTNB and Thimersosol but not with iodo-acetate
34	Alternative splice site	Insertion reduces biological activity
20-47 (inclusive)	Helix A, first disulfide and portion of AB helix	Predicted receptor binding region based on neutralizing antibody data
20, 23, 24	Helix A	Single alanine mutation of residue(s) reduces biological activity. Predicted receptor binding (Site B).
165-175 (inclusive)	Carboxy terminus	Deletion reduces biological activity

[0061] This biochemical information, having been gleaned from antibody binding studies, see Layton et al., Biochemistry 266: 23815-23823 (1991), was superimposed on the three-dimensional structure in order to design G-CSF analogs. The design, preparation, and testing of these G-CSF analogs is described in Example 1 below.

EXAMPLE 1

[0062] This Example describes the preparation of crystalline G-CSF, the visualization of the three dimensional structure of recombinant human G-CSF via computer-generated image, the preparation of analogs, using site-directed mutagenesis or nucleic acid amplification methods, the biological assays and HPLC analysis used to analyze the G-CSF analogs, and the resulting determination of overall structure/function relationships. All cited publications are herein incorporated by reference.

A. Use of Automated Crystallization

[0063] The need for a three-dimensional structure of recombinant human granulocyte colony stimulating factor (r-hu-G-CSF), and the availability of large quantities of the purified protein, led to methods of crystal growth by incomplete factorial sampling and seeding. Starting with the implementation of incomplete factorial crystallization described by Jancarik and Kim· J. Appl. Crystallogr. 24: 409 (1991) solution conditions that yielded oil droplets and birefringence aggregates were ascertained. Also, software and hardware of an automated pipetting system were modified to produce some 400 different crystallization conditions per day. Weber, J. Appl. Crystallogr. 20: 366-373 (1987). This procedure led to a crystallization solution which produced r-hu-G-CSF crystals.

[0064] The size, reproducibility and quality of the crystals was improved by a seeding method in which the number of "nucleation initiating units" was estimated by serial dilution of a seeding solution. These methods yielded reproducible growth of 2.0 mm r-hu-G-CSF crystals. The space group of these crystals is $P2_12_12_1$ with cell dimensions of a=90 Å, b=110 Å and c=49 Å, and they diffract to a resolution of 2.0 Å.

1. Overall Methodology

[0065] To search for the crystallizing conditions of a new protein, Carter and Carter, J. Biol. Chem. 254: 12219-12223 (1979) proposed the incomplete factorial method. They suggested that a sampling of a large number of randomly selected, but generally probable, crystallizing conditions may lead to a successful combination of reagents that produce protein crystallization. This idea was implemented by Jancarik and Kim, J. Appl. Crystallogr. 24: 409(1991), who described 32 solutions for the initial crystallization trials which cover a range of pH, salts and precipitants. Here we describe an extension of their implementation to an expanded set of 70 solutions. To minimize the human effort and error of solution preparation, the method has been programmed for an automatic pipetting machine.

[0066] Following Weber's method of successive automated grid searching (SAGS), J.Cryst. Growth 90: 318-324(1988), the robotic system was used to generate a series of solutions which continually refined the crystallization conditions of temperature, pH, salts and precipitant. Once a solution that could reproducibly grow crystals was determined, a seeding technique which greatly improved the quality of the crystals was developed. When these methods were combined, hundreds of diffraction quality crystals (crystals diffracting to at least about 2.5 Angstroms, preferably having at least portions diffracting to below 2 Angstroms, and more preferably, approximately 1 Angstrom) were produced in a few days.

[0067] Generally, the method for crystallization, which may be used with any protein one desires to crystallize, comprises the steps of:

(a) combining aqueous aliquots of the desired protein with either (i) aliquots of a salt solution, each aliquot having a different concentration of salt; or (ii) aliquots of a precipitant solution, each aliquot having a different concentration of precipitant, optionally wherein each combined aliquot is combined in the presence of a range of pH;
(b) observing said combined aliquots for precrystalline formations, and selecting said salt or precipitant combination and said pH which is efficacious in producing precrystalline forms, or, if no precrystalline forms are so produced, increasing the protein starting concentration of said aqueous aliquots of protein;
(c) after said salt or said precipitant concentration is selected, repeating step (a) with said previously unselected solution in the presence of said selected concentration; and
(d) repeating step (b) and step (a) until a crystal of desired quality is obtained.

[0068] The above method may optionally be automated, which provides vast savings in time and labor. Preferred protein starting concentrations are between 10mg/ml and 20mg/ml, however this starting concentration will vary with the protein (the G-CSF below was analyzed using 33mg/ml). A preferred range of salt solution to begin analysis with is

(NaCl) of 0-2.5M. A preferred precipitant is polyethylene glycol 8000, however, other precipitants include organic solvents (such as ethanol), polyethylene glycol molecules having a molecular weight in the range of 500-20,000, and other precipitants known to those skilled in the art. The preferred pH range is pH 4.5 , 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, and 9.0. Precrystallization forms include oils, birefringement precipitants, small crystals (< approximately 0.05 mm), medium crystals (approximately 0.5 to .5 mm) and large crystals (> approximately 0.5 mm). The preferred time for waiting to see a crystalline structure is 48 hours, although weekly observation is also preferred, and generally, after about one month, a different protein concentration is utilized (generally the protein concentration is increased). Automation is preferred, using the Accuflex system as modified. The preferred automation parameters are described below.

[0069] Generally, protein with a concentration between 10 mg/ml and 20 mg/ml was combined with a range of NaCl solutions from 0-2.5 M, and each such combination was performed (separately) in the presence of the above range of concentrations. Once a precrystallization structure is observed, that salt concentration and pH range are optimized in a separate experiment, until the desired crystal quality is achieved. Next, the precipitant concentration, in the presence of varying levels of pH is also optimized. When both are optimized, the optimal conditions are performed at once to achieve the desired result (this is diagrammed in FIGURE 6).

a. Implementation of an automated pipetting system

[0070] Drops and reservoir solutions were prepared by an Accuflex pipetting system (ICN Pharmaceuticals, Costa Mesa, CA) which is controlled by a personal computer that sends ASCII codes through a standard serial interface. The pipetter samples six different solutions by means of a rotating valve and pipettes these solutions onto a plate whose translation in a x-y coordinate system can be controlled. The vertical component of the system manipulates a syringe that is capable both of dispensing and retrieving liquid.

[0071] The software provided with the Accuflex was based on the SAGS method as proposed by Cox and Weber, J.Appl. Crystallogr. 20: 366-373 (1987). This method involves the systematic variation of two major crystallization parameters, pH and precipitant concentration, with provision to vary two others. While building on these concepts, the software used here provided greater flexibility in the design and implementation of the crystallization solutions used in the automated grid searching strategy. As a result of this flexibility the present software also created a larger number of different solutions. This is essential for the implementation of the incomplete factorial method as described in that section below.

[0072] To improve the speed and design of the automated grid searching strategy, the Accuflex pipetting system required software and hardware modifications. The hardware changes allowed the use of two different micro-titer trays, one used for handing drop and one used for sitting drop experiments, and a Plexiglas tray which held 24 additional buffer, salt and precipitant solutions. These additional solutions expanded the grid of crystallizing conditions that could be surveyed.

[0073] To utilize the hardware modifications, the pipetting software was written in two subroutines; one subroutine allows the crystallographer to design a matrix of crystallization solutions based on the concentrations of their components and the second subroutine to translate these concentrations into the computer code which pipettes the proper volumes of the solutions into the crystallization trays. The concentration matrices can be generated by either of two programs. The first program (MRF, available from Amgen, Inc., Thousand Oaks, CA) refers to a list of stock solution concentrations supplied by the crystallographer and calculates the required volume to be pipette to achieve the designated concentration. The second method, which is preferred, incorporates a spread sheet program (Lotus) which can be used to make more sophisticated gradients of precipitants or pH. The concentration matrix created by either program is interpreted by the control program (SUX, a modification of the program found in the Accuflex pipetter originally and available from Amgen, Inc., Thousand Oaks, CA) and the wells are filled accordingly.

b. Implementation of the Incomplete Factorial Method

[0074] The convenience of the modified pipetting system for preparing diverse solutions improved the implementation of an expanded incomplete factorial method. The development of a new set of crystallization solutions having "random" components was generated using the program INFAC, Carter et al., J.Cryst. Growth 90: 60-73(1988) which produced a list containing 96 random combinations of one factor from three variables. Combinations of calcium and phosphate which immediately precipitated were eliminated, leaving 70 distinct combinations of precipitants, salts and buffers. These combinations were prepared using the automated pipetter and incubated for 1 week. The mixtures were inspected and solutions which formed precipitants were prepared again with lower concentrations of their components. This was repeated until all wells were clear of precipitant.

c. Crystallization of r-hu-G-CSF

[0075] Several different crystallization strategies were used to find a solution which produced x-ray quality crystals. These strategies included the use of the incomplete factorial method, refinement of the crystallization conditions using successive automated grid searches (SAGS), implementation of a seeding technique and development of a crystal production procedure which yielded hundreds of quality crystals overnight. Unless otherwise noted the screening and production of r-hu-G-CSF crystals utilized the hanging drop vapor diffusion method. Afinsen et al., Physical principles of protein crystallization. In: Eisenberg (ed.), Advances in Protein Chemistry 41: 1-33 (1991).

[0076] The initial screening for crystallization conditions of r-hu-G-CSF used the Jancarik and Kim, J.Appl.Crystallogr. 24: 409(1991) incomplete factorial method which resulted in several solutions that produced "precrystallization" results. These results included birefringent precipitants, oils and very small crystals (< .05 mm). These precrystallizations solutions then served as the starting points for systematic screening.

[0077] The screening process required the development of crystallization matrices. These matrices corresponded to the concentration of the components in the crystallization solutions and were created using the IBM-PC based spread sheet Lotus™ and implemented with the modified Accuflex pipetting system. The strategy in designing the matrices was to vary one crystallization condition (such as salt concentration) while holding the other conditions such as pH, and precipitant concentration constant. At the start of screening, the concentration range of the varied condition was large but the concentration was successively refined until all wells in the micro-titer tray produced the same crystallization result. These results were scored as follows: crystals, birefringement precipitate, granular precipitate, oil droplets and amorphous mass. If the concentration of a crystallization parameter did not produce at least a precipitant, the concentration of that parameter was increased until a precipitant formed. After each tray was produced, it was left undisturbed for at least two days and then inspected for crystal growth. After this initial screening, the trays were then inspected on a weekly basis.

[0078] From this screening process, two independent solutions with the same pH and precipitant but differing in salts ($MgCl$, $LiSO_4$) were identified which produced small (0.1 x 0.05 x 0.05 mm) crystals. Based on these results, a new series of concentration matrices were produced which varied $MgCl$ with respect to $LiSO_4$ while keeping the other crystallization parameters constant. This series of experiments resulted in identification of a solution which produced diffraction quality crystals (> approximately 0.5 mm) in about three weeks. To find this crystallization growth solution (100 mM Mes pH 5.8, 380 mM $MgCl_2$, 220 mM LiSO4 and 8% PEG 8k) approximately 8,000 conditions had been screened which consumed about 300 mg of protein.

[0079] The size of the crystals depended on the number of crystals forming per drop. Typically 3 to 5 crystals would be formed with average size of (1.0 x 0.7 x 0.7 mm). Two morphologies which had an identical space group ($P2_12_12_1$) and unit cell dimensions a=90.2, b=110.2, c=49.5 were obtained depending on whether or not seeding (see below) was implemented. Without seeding, the r-hu-G-CSF crystals had one long flat surface and rounded edges.

[0080] When seeding was employed, crystals with sharp faces were observed in the drop within 4 to 6 hours (0.05 by 0.05 by 0.05 mm). Within 24 hours, crystals had grown to (0.7 by 0.7 by 0.7 mm) and continued to grow beyond 2 mm depending on the number of crystals forming in the drop.

d. Seeding and determination of nucleation initiation sites.

[0081] The presently provided method for seeding crystals establishes the number of nucleation initiation units in each individual well used (here, after the optimum conditions for growing crystals had been determined). The method here is advantageous in that the number of "seeds" affects the quality of the crystals, and this in turn affects the degree of resolution. The present seeding here also provides advantages in that with seeding, G-CSF crystal grows in a period of about 3 days, whereas without seeding, the growth takes approximately three weeks.

[0082] In one series of production growth (see methods), showers of small but well defined crystals were produced overnight (<0.01 x 0.01 x0.01 mm). Crystallization conditions were followed as described above except that a pipette tip employed in previously had been reused. Presumably, the crystal showering effect was caused by small nucleation units which had formed in the used tip and which provided sites of nucleation for the crystals. Addition of a small amount (0.5 ul) of the drops containing the crystal showers to a new drop under standard production growth conditions resulted in a shower of crystals overnight. This method was used to produce several trays of drops containing crystal showers which we termed "seed stock".

[0083] The number of nucleation initiation units (NIU) contained within the "seed stock" drops was estimated to attempt to improve the reproducibility and quality of the r-hu-GCSF crystals. To determine the number of NIU in the "seed stock", an aliquot of the drop was serially diluted along a 96 well microtiter plate. The microtiter plate was prepared by adding 50 ul of a solution containing equal volumes of r-hu-G-CSF (33 mg/ml) and the crystal growth solution (described above) in each well. An aliquot (3 ul) of one of the "seed stock" drops was transferred to the first well of the microtiter plate. The solution in the well was mixed and 3 ul was then transferred to the next well along the row of the

microtiter plate. Each row of the microtiter plate was similarly prepared and the tray was sealed with plastic tape. Overnight, small crystals formed in the bottom of the wells of the microtiter plate and the number of crystals in the wells were correlated to the dilution of the original "seed stock". To produce large single crystals, the "seed stock" drop was appropriately diluted into fresh CGS and then an aliquot of this solution containing the NIU was transferred to a drop

[0084] Once crystallization conditions had been optimized, crystals were grown in a production method in which 3 ml each of CGS and r-hu-G-CSF (33 mg/ml) were mixed to create 5 trays (each having 24 wells). This method included the production of the refined crystallization solution in liter quantities, mixing this solution with protein and placing the protein/crystallization solution in either hanging drop or sitting drop trays. This process typically yielded 100 to 300 quality crystals (>0.5 mm) in about 5 days.

e. Experimental Methods

Materials

[0085] Crystallographic information was obtained starting with r-hu-met-G-CSF with the amino acid sequence as provided in FIGURE 1 with a specific activity of 1.0 +/- 0.6 x 10^8U/mg (as measured by cell mitogenesis assay in a 10 mM acetate buffer at pH 4.0 (in Water for Injection) at a concentration of approximately 3 mg/ml solution was concentrated with an Amicon concentrator at 75 psi using a YM10 filter. The solution was typically concentrated 10 fold at 4°C and stored for several months.

Initial Screening

[0086] Crystals suitable for X-ray analysis were obtained by vapor-diffusion equilibrium using hanging drops. For preliminary screening, 7 ul of the protein solution at 33 mg/ml (as prepared above) was mixed with an equal volume of the well solution, placed on siliconized glass plates and suspended over the well solution utilizing Linbro tissue culture plates (Flow Laboratories, McLean, Va). All of the pipetting was performed with the Accuflex pipetter, however, trays were removed from the automated pipetter after the well solutions had been created and thoroughly mixed for at least 10 minutes with a table top shaker. The Linbro trays were then returned to the pipetter which added the well and protein solutions to the siliconized cover slips. The cover slips were then inverted and sealed over 1 ml of the well solutions with silicon grease.

[0087] The components of the automated crystallization system are as follows. A PC-DOS computer system was used to design a matrix of crystallization solutions based on the concentration of their components. These matrices were produced with either MRF of the Lotus spread sheet (described above). The final product of these programs is a data file. This file contains the information required by the SUX program to pipette the appropriate volume of the stock solutions to obtain the concentrations described in the matrices. The SUX program information was passed through a serial I/O port and used to dictate to the Accuflex pipetting system the position of the valve relative to the stock solutions, the amount of solution to be retrieved, and then pipetted into the wells of the microtiter plates and the X-Y position of each well (the column/row of each well). Addition information was transmitted to the pipetter which included the Z position (height) of the syringe during filling as well as the position of a drain where the system pauses to purge the syringe between fillings of different solutions. The 24 well microtiter plate (either Linbro or Cryschem) and cover slip holder was placed on a plate which was moved in the X-Y plane. Movement of the plate allowed the pipetter to position the syringe to pipette into the wells. It also positioned the coverslips and vials and extract solutions from these sources. Prior the pipetting, the Linbro microtiter plates had a thin film of grease applied around the edges of the wells. After the crystallization solutions were prepared in the wells and before they were transferred to the cover slips, the microtiter plate was removed from the pipetting system, and solutions were allowed to mix on a table top shaker for ten minutes. After mixing, the well solution was either transferred to the cover slips (in the case of the hanging drop protocol) or transferred to the middle post in the well (in the case of the sitting drop protocol). Protein was extracted from a vial and added to the coverslip drop containing the well solution (or to the post). Plastic tape was applied to the top of the Cryschem plate to seal the wells.

Production Growth

[0088] Once conditions for crystallization had been optimized, crystal growth was performed utilizing a "production" method. The crystallization solution which contained 100 mM Mes pH 5.8, 380 mM $MgCl_2$, 220 mM $LiSO_4$, and 8% PEG 8K was made in 1 liter quantities. Utilizing an Eppindorf syringe pipetter, 1 ml aliquots of this solution were pipetted into each of the wells of the Linbro plate. A solution containing 50% of this solution and 50% G-CSF (33 mg/ml) was mixed and pipetted onto the siliconized cover slips. Typical volumes of these drops were between 50 and 100 ul and because of the large size of these drops, great care was taken in flipping the coverslips and suspending the drops over

the wells.

Data Collection

[0089] The structure has been refined with X-PLOR (Bruniger, X-PLOR version 3.0, A system for crystallography and NMR, Yale University, New Haven CT) against 2.2Å data collected on an R-AXIS (Molecular Structure, Corp. Houston, TX) imaging plate detector.

f. Observations

[0090] As an effective recombinant human therapeutic, r-hu-G-CSF has been produced in large quantities and gram levels have been made available for structural analysis. The crystallization methods provided herein are likely to find other applications as other proteins of interest become available. This method can be applied to any crystallographic project which has large quantities of protein (approximately >200 mg). As one skilled in the art will recognize, the present materials and methods may be modified and equivalent materials and methods may be available for crystallization of other proteins.

B. Computer Program For Visualizing The Three Dimensional Structure of G-CSF

[0091] Although diagrams, such as those in the Figures herein, are useful for visualizing the three dimensional structure of G-CSF, a computer program which allows for stereoscopic viewing of the molecule is contemplated as preferred. This stereoscopic viewing, or "virtual reality" as those in the art sometimes refer to it, allows one to visualize the structure in its three dimensional form from every angle in a wide range of resolution, from macromolecular structure down to the atomic level. The computer programs contemplated herein also allow one to change perspective of the viewing angle of the molecule, for example by rotating the molecule. The contemplated programs also respond to changes so that one may, for example, delete, add, or substitute one or more images of atoms, including entire amino acid residues, or add chemical moieties to existing or substituted groups, and visualize the change in structure.

[0092] Other computer based systems may be used; the elements being: (a) a means for entering information, such as orthogonal coordinates or other numerically assigned coordinates of the three dimensional structure of G-CSF; (b) a means for expressing such coordinates, such as visual means so that one may view the three dimensional structure and correlate such three dimensional structure with the composition of the G-CSF molecule, such as the amino acid composition; (c) optionally, means for entering information which alters the composition of the G-CSF molecule expressed, so that the image of such three dimensional structure displays the altered composition.

[0093] The coordinates for the preferred computer program used are presented in FIGURE 5. The preferred computer program is Insight II, version 4, available from Biosym in San Diego, CA. For the raw crystallographic structure, the observed intensities of the diffraction data ("F-obs") and the orthogonal coordinates are also deposited in the Protein Data Bank, Chemistry Department, Brookhaven National Laboratory, Upton, New York 19723, USA and these are herein incorporated by reference.

[0094] Once the coordinates are entered into the Insight II program, one can easily display the three dimensional G-CSF molecule representation on a computer screen. The preferred computer system for display is Silicon Graphics 320 VGX (San Diego, CA). For stereoscopic viewing, one may wear eyewear (Crystal Eyes, Silicon Graphics) which allows one to visualize the G-CSF molecule in three dimensions stereoscopically, so one may turn the molecule and envision molecular design.

[0095] Thus, the present invention provides a method of designing or preparing a G-CSF analog with the aid of a computer comprising:

(a) providing said computer with the means for displaying the three dimensional structure of a G-CSF molecule including displaying the composition of moieties of said G-CSF molecule, preferably displaying the three dimensional location of each amino acid, and more preferably displaying the three dimensional location of each atom of a G-CSF molecule;
(b) viewing said display;
(c) selecting a site on said display for alteration in the composition of said molecule or the location of a moiety; and
(d) preparing a G-CSF analog with such alteration.

[0096] The alteration may be selected based on the desired structural characteristics of the end-product G-CSF analog, and considerations for such design are described in more detail below. Such considerations include the location and compositions of hydrophobic amino acid residues, particularly residues internal to the helical structures of a G-CSF molecule which residues, when altered, alter the overall structure of the internal core of the molecule and may prevent

receptor binding; the location and compositions of external loop structures, alteration of which may not affect the overall structure of the G-CSF molecule.

[0097] FIGURES 2-4 illustrate the overall three dimensional conformation in different ways. The topological diagram, the ribbon diagram, and the barrel diagram all illustrate aspects of the conformation of G-CSF.

[0098] FIGURE 2 illustrates a comparison between G-CSF and other molecules. There is a similarity of architecture, although these growth factors differ in the local conformations of their loops and bundle geometrics. The up-up-down-down topology with two long crossover connections is conserved, however, among all six of these molecules, despite the dissimilarity in amino acid sequence.

[0099] FIGURE 3 illustrates in more detail the secondary structure of recombinant human G-CSF. This ribbon diagram illustrates the handedness of the helices and their positions relative to each other.

[0100] FIGURE 4 illustrates in a different way the conformation of recombinant human G-CSF. This "barrel" diagram illustrates the overall architecture of recombinant human G-CSF.

C. Preparation of Analogs Using M13 Mutagenesis

[0101] This example relates to the preparation of G-CSF analogs using site directed mutagenesis techniques involving the single stranded bacteriophage M13, according to methods published in PCT Application No. WO 85/00817 (Souza et al., published February 28, 1985, herein incorporated by reference). This method essentially involves using a single-stranded nucleic acid template of the non-mutagenized sequence, and binding to it a smaller oligonucleotide containing the desired change in the sequence. Hybridization conditions allow for non-identical sequences to hybridize and the remaining sequence is filled in to be identical to the original template. What results is a double stranded molecule, with one of the two strands containing the desired change. This mutagenized single strand is separated, and used itself as a template for its complementary strand. This creates a double stranded molecule with the desired change.

[0102] The original G-CSF nucleic acid sequence used is presented in FIGURE 1, and the oligonucleotides containing the mutagenized nucleic acid(s) are presented in Table 2. Abbreviations used herein for amino acid residues and nucleotides are conventional, see Stryer, Biochemistry, 3d Ed., W.H. Freeman and Company, N.Y., N.Y. 1988, inside back cover.

[0103] The original G-CSF nucleic acid sequence was first placed into vector M13mp21. The DNA from single stranded phage M13mp21 containing the original G-CSF sequence was then isolated, and resuspended in water. For each reaction, 200 ng of this DNA was mixed with a 1.5 pmole of phosphorylated oligonucleotide (Table 2) and suspended in 0.1M Tris, 0.01M $MgCl_2$, 0.005M DTT, 0.1mM ATP, pH 8.0. The DNAs were annealed by heating to 65°C and slowly cooling to room temperature.

[0104] Once cooled, 0.5mM of each ATP, dATP, dCTP, dGTP, TTP, 1 unit of T4 DNA ligase and 1 unit of Klenow fragment of E. coli polymerase 1 were added to the 1 unit of annealed DNA in 0.1M Tris, 0.025M NaCl, 0.01M $MgCl_2$, 0.01M DTT, pH 7.5.

[0105] The now double stranded, closed circular DNA was used to transfect E. coli without further purification. Plaques were screened by lifting the plaques with nitrocellulose filters, and then hybridizing the filters with single stranded DNA end-labeled with P^{32} for 1 hour at 55-60°C. After hybridization, the filters were washed at 0-3°C below the melt temperature of the oligo (2°C for A-T, 4°C for G-C) which selectively left autoradiography signals corresponding to plaques with phage containing the mutated sequence. Positive clones were confirmed by sequencing.

[0106] Set forth below are the oligonucleotides used for each G-CSF analog prepared via the M13 mutagenesis method. The nomenclature indicates the residue and the position of the original amino acid (e.g., Lysine at position 17), and the residue and position of the substituted amino acid (e.g., arginine 17). A substitution involving more than one residue is indicated via superscript notation, with commas between the noted positions or a semicolon indicating different residues. Deletions with no substitutions are so noted. The oligonucleotide sequences used for M13-based mutagenesis are next indicated; these oligonucleotides were manufactured synthetically, although the method of preparation is not critical, any nucleic acid synthesis method and/or equipment may be used. The length of the oligo is also indicated. As indicated above, these oligos were allowed to contact the single stranded phage vector, and then single nucleotides were added to complete the G-CSF analog nucleic acid sequence.

Table 2

G-CSF ANALOGS	SEQUENCES(5'-> 3')	Length(nucleotide)	Seq. ID
Lys^{17}->Arg^{17}	CTT TCT GCT GCG TTG TCT GGA ACA	24	3
Lys^{24}->Arg^{24}	ACA GGT TCG TCG TAT CCA GGG TG	23	4
Lys^{35}->Arg^{35}	CAC TGC AAG AAC GTC TGT GCG CT	23	5
Lys^{41}->Arg^{41}	CGC TAC TTA CCG TCT GTG CCA TC	23	6
$Lys^{17,24,35}$->	CTT TCT GCT GCG TTG TCT GGA ACA	24	7
$Arg^{17,24,35}$	ACA GGT TCG TCG TAT CCA GGG TG	23	8
	CAC TGC AAG AAC GTC TGT GCG CT	23	9
$Lys^{17,24,41}$->	CTT TCT GCT GCG TTG TCT GGA ACA	24	10
$Arg^{17,24,41}$	ACA GGT TCG TCG TAT CCA GGG TG	23	11
	CGC TAC TTA CCG TCT GTC CCA TC	23	12
$Lys^{17,35,41}$->	CTT TCT GCT GCG TTG TCT GGA ACA	24	13
$Arg^{17,35,41}$	CAC TGC AAG AAC GTC TGT GCG CT	23	14
	CGC TAC TTA CCG TCT GTG CCA TC	23	15
$Lys^{24,35,41}$->	ACA GGT TCG TCG TAT CCA GGG TG	23	16
$Arg^{24,35,41}$	CAC TGC AAG AAC GTC TGT GCG CT	23	17
	CGC TAC TTA CCG TCT GTG CCA TC	23	18

Table 2 (con't)

G-CSF ANALOGS	SEQUENCES (5'-> 3')	Length (nucleotide)	Seq. ID
$Lys^{17,24,35,41}$-> $Arg^{17,24,35,41}$	CTT TCT GCT GCG TTG TCT GGA ACA	24	19
	ACA GGT TCG TCG TAT CCA GGG TG	23	20
	CAC TGC AAG AAC GTC TGT GCG CT	23	21
	CGC TAC TTA CCG TCT GTG CCA TC	23	22
Cys^{18}->Ala^{18}	TCT GCT GAA AGC TCT GGA ACA GG	23	23
Gln^{68}->Glu^{68}	CTT GTC CAT CTG AAG CTC TTC AG	23	24
$Cys^{37,43}$-> $Ser^{37,43}$	GAA AAA CTG TCC GCT ACT TAC AAA CTG TCC CAT CCG G	37	25
Gln^{26}->Ala^{26}	TTC GTA AAA TCG CGG GTG ACG G	22	26
Gln^{174}->Ala^{174}	TCA TCT GGC TGC GCC GTA ATA G	22	27
Arg^{170}->Ala^{170}	CCG TGT TCT GGC TCA TCT GGC T	22	28
Arg^{167}->Ala^{167}	GAA GTA TCT TAC GCT GTT CTG CGT	24	29
Deletion 167	GAA GTA TCT TAC TAA GTT CTG CGT C	25	30
Lys^{41}->Ala^{41}	CGC TAC TTA CGC ACT GTG CCA T	22	31
His^{44}->Lys^{44}	CAA ACT GTG CAA GCC GGA AGA G	22	32
Glu^{47}->Ala^{47}	CAT CCG GAA GCA CTG GTA CTG C	22	33

EP 0 612 846 B1

Table 2 (con't)

G-CSF ANALOGS	SEQUENCES(5'-> 3')	Length(nucleotide)	Seq. ID
Arg^{23}->Ala^{23}	GGA ACA GGT TGC TAA AAT CCA GG	23	34
Lys^{24}->Ala^{24}	GAA CAG GTT CGT GCG ATC CAG GGT G	25	35
Glu^{20}->Ala^{20}	GAA ATG TCT GGC ACA GGT TCG T	22	36
Asp^{28}->Ala^{28}	TCC AGG GTG CCG GTG CTG C	19	37
Met^{127}->Glu^{127}	AAG AGC TCG GTG AGG CAC CAG CT	23	38
Met^{138}->Glu^{138}	CTC AAG GTG CTG AGC CGG CAT TC	23	39
Met^{127}->Leu^{127}	GAG CTC GGT CTG GCA CCA GC	20	40
Met^{138}->Leu^{138}	TCA AGG TGC TCT GCC GGC ATT	21	41
Ser^{13}->Ala^{13}	TCT GCC GCA AGC CTT TCT GCT GA	23	42
Lys^{17}->Ala^{17}	CTT TCT GCT GGC ATG TCT GGA ACA	24	43
Gln^{121}->Ala^{121}	CTA TTT GGC AAG CGA TGG AAG AGC	24	44
Glu^{124}->Ala^{124}	CAG ATG GAA GCG CTC GGT ATG	21	45

EP 0 612 846 B1

Table 2 (con't)

G-CSF ANALOGS	SEQUENCES (5'-> 3')	Length (nucleotide)	Seq. ID
$Met^{127,138}$-> $Leu^{127,138}$	GAG CTC GGT CTG GCA CCA GC	20	46
	TCA AGG TGC TCT GCC GGC ATT	21	47
**Glu^{20}->Ala^{20}; Ser^{13}->Gly^{13}	GAA ATG TCT GGC ACA GGT TCG T	22	48

** This analog came about during the preparation of G-CSF analog Glu^{20}->Ala^{20}. As several clones were being sequenced to identify the Glu^{20}->Ala^{20} analog, the Glu^{20}->Ala^{20}; Ser^{13}->Gly^{13} analog was identified. This double mutant was the result of an *in vitro* Klenow DNA polymerase reaction mistake.

D. Preparation of G-CSF Analogs Using DNA Amplification

[0107] This example relates to methods for producing G-CSF analogs using a DNA amplification technique. Essentially, DNA encoding each analog was amplified in two separate pieces, combined, and then the total sequence itself amplified. Depending upon where the desired change in the original G-CSF DNA was to be made, internal primers were used to incorporate the change, and generate the two separate amplified pieces. For example, for amplification of the 5' end of the desired analog DNA, a 5' flanking primer (complementary to a sequence of the plasmid upstream from the G-CSF original DNA) was used at one end of the region to be amplified, and an internal primer, capable of hybridizing to the original DNA but incorporating the desired change, was used for priming the other end. The resulting amplified region stretched from the 5' flanking primer through the internal primer. The same was done for the 3' terminus, using a 3' flanking primer (complementary to a sequence of the plasmid downstream from the G-CSF original DNA) and an internal primer complementary to the region of the intended mutation. Once the two "halves" (which may or may not be equal in size, depending on the location of the internal primer) were amplified, the two "halves" were allowed to connect. Once connected, the 5' flanking primer and the 3' flanking primer were used to amplify the entire sequence containing the desired change.

[0108] If more than one change is desired, the above process may be modified to incorporate the change into the internal primer, or the process may be repeated using a different internal primer. Alternatively, the gene amplification process may be used with other methods for creating changes in nucleic acid sequence, such as the phage based mutagenesis technique as described above. Examples of process for preparing analogs with more than one change are described below.

[0109] To create the G-CSF analogs described below, the template DNA used was the sequence as in FIGURE 1 plus certain flanking regions (from a plasmid containing the G-CSF coding region). These flanking regions were used as the 5' and 3' flanking primers and are set forth below. The amplification reactions were performed in 40 ul volumes containing 10 mM Tris-HCl, 1.5 mM $MgCl_2$, 50 mM KCl, 0.1 mg/ml gelatin, pH 8.3 at 20°C. The 40 ul reactions also contained 0.1mM of each dNTP, 10 pmoles of each primer, and 1 ng of template DNA. Each amplification was repeated for 15 cycles. Each cycle consisted of 0.5 minutes at 94°C, 0.5 minutes at 50°C, and 0.75 minutes at 72°C. Flanking primers were 20 nucleotides in length and internal primers were 20 to 25 nucleotides in length. This resulted in multiple copies of double stranded DNA encoding either the front portion or the back portion of the desired G-CSF analog.

[0110] For combining the two "halves," one fortieth of each of the two reactions was combined in a third DNA amplification reaction. The two portions were allowed to anneal at the internal primer location, as their ends bearing the mutation were complementary, and following a cycle of polymerization, give rise to a full length DNA sequence. Once so annealed, the whole analog was amplified using the 5' and 3' flanking primers. This amplification process was repeated for 15 cycles as described above.

[0111] The completed, amplified analog DNA sequence was cleaved with XbaI and XhoI restriction endonuclease to produce cohesive ends for insertion into a vector. The cleaved DNA was placed into a plasmid vector, and that vector was used to transform E. coli. Transformants were challenged with kanamycin at 50 ug/ml and incubated at 30°C. Production of G-CSF analog protein was confirmed by polyacrylamide gel electrophoresis of a whole cell lysate. The presence of the desired mutation was confirmed by DNA sequence analysis of plasmid purified from the production isolate. Cultures were then grown, and cells were harvested, and the G-CSF analogs were purified as set forth below.

[0112] Set forth below in Table 3 are the specific primers used for each analog made using gene amplification.

Table 3

Analog Seq. ID	Internal Primer(5'->3')	
His^{44}->Ala^{44}	5'primer-TTCCGGAGCGCACAGTTTG	49
	3'primer-CAAACTGTGGGCTCCGGAAGAGC	50
Thr^{117}->Ala^{117}	5'primer-ATGCCAAATTGCAGTAGCAAAG	51
	3'primer-CTTTGCTACTGCAATTTGGCAACA	52
Asp^{110}->Ala^{110}	5'primer-ATCAGCTACTGCTAGCTGCAGA	53
	3'primer-TCTGCAGCTAGCAGTAGCTGACT	54
Gln^{21}->Ala^{21}	5'primer-TTACGAACCGCTTCCAGACATT	55
	3'primer-AATGTCTGGAAGCGGTTCGTAAAAT	56

Table 3 (continued)

Analog Seq. ID	Internal Primer(5'->3')	
Asp^{113}->Ala^{113}	5'primer-GTAGCAAATGCAGCTACATCTA	57
	3'primer-TAGATGTAGCTGCATTTGCTACTAC	58
His^{53}->Ala^{53}	5'primer-CCAAGAGAAGCACCCAGCAG	59
	3'primer-CTGCTGGGTGCTTCTCTTGGGA	60
For each analog, the following 5' flanking primer was used:		
	5'-CACTGGCGGTGATAATGAGC	61
For each analog, the following 3' flanking primer was used:		
	3'-GGTCATTACGGACCGGATC	62

1. Construction of Double Mutation

[0113] To make G-CSF analog $Gln^{12,21}$->$Glu^{12,21}$, two separate DNA amplifications were conducted to create the two DNA mutations. The template DNA used was the sequence as in FIGURE 1 plus certain flanking regions (from a plasmid containing the G-CSF coding region). The precise sequences are listed below. Each of the two DNA amplification reactions were carried out using a Perkin Elmer/Cetus DNA Thermal Cycler. The 40 ul reaction mix consisted of 1X PCR Buffer (Cetus), 0.2 mM each of the 4 dXTPs (Cetus), 50 pmoles of each primer oligonucleotide, 2 ng of G-CSF template DNA (on a plasmid vector), and 1 unit of Taq polymerase (Cetus). The amplification process was carried out for 30 cycles. Each cycle consisted of 1minute at 94°C, 2 minutes at 50°C, and 3 minutes at 72°C.

[0114] DNA amplification "A" used the oligonucleotides:
5' CCACTGGCGGTGATACTGAGC 3' (Seq. ID 63) and
5' AGCAGAAAGCTTTCCGGCAGAGAAGAAGCAGGA 3' (Seq. ID 64)

[0115] DNA amplification "B" used the oligonucleotides:
5' GCCGCAAAGCTTTCTGCTGAAATGTCTGGAAGAGGTTCGTAAAATCCAGGGTGA 3' (Seq. ID 65) and
5' CTGGAATGCAGAAGCAAATGCCGGCATAGCACCTTCAGTCGGTTGCAGAGCTGGTGCCA 3' (Seq. ID 66)

[0116] From the 109 base pair double stranded DNA product obtained after DNA amplification "A", a 64 base pair XbaI to HindIII DNA fragment was cut and isolated that contained the DNA mutation Gln^{12}->Glu^{12}. From the 509 base pair double stranded DNA product obtained after DNA amplification "B", a 197 base pair HindIII to BsmI DNA fragment was cut and isolated that contained the DNA mutation Gln^{21}->Glu^{21}.

[0117] The "A" and "B" fragments were ligated together with a 4.8 kilo-base pair XbaI to BsmI DNA plasmid vector fragment. The ligation mix consisted of equal molar DNA restriction fragments, ligation buffer (25 mM Tris-HCl pH 7.8, 10 mM $MgCl_2$, 2 mM DTT, 0.5 mM rATP, and 100 ug/ml BSA) and T4 DNA ligase and was incubated overnight at 14°C. The ligated DNA was then transformed into E. coli FM5 cells by electroporation using a Bio Rad Gene Pulsar apparatus (BioRad, Richmond, CA). A clone was isolated and the plasmid construct verified to contain the two mutations by DNA sequencing. This 'intermediate' vector also contained a deletion of a 193 base pair BsmI to BsmI DNA fragment. The final plasmid vector was constructed by ligation and transformation (as described above) of DNA fragments obtained by cutting and isolating a 2 kilo-base pair SstI to BamHI DNA fragment from the intermediate vector, a 2.8 kbp SstI to EcoRI DNA fragment from the plasmid vector, and a 360 bp BamHI to EcoRI DNA fragment from the plasmid vector. The final construct was verified by DNA sequencing the G-CSF gene. Cultures were grown, and the cells were harvested, and the G-CSF analogs were purified as set forth below.

[0118] As indicated above, any combination of mutagenesis techniques may be used to generate a G-CSF analog nucleic acid (and expression product) having one or more than one alteration. The two examples above, using M13-based mutagenesis and gene amplification-based mutagenesis, are illustrative.

E. Expression of G-CSF Analog DNA

[0119] The G-CSF analog DNAs were then placed into a plasmid vector and used to transform E. coli strain FM5 (ATCC#53911). The present G-CSF analog DNAs contained on plasmids and in bacterial host cells are available from the American Type Culture Collection, Rockville, MD, and the accession designations are indicated below.

[0120] One liter cultures were grown in broth containing 10g tryptone, 5g yeast extract and 5g NaCl) at 30°C until reaching a density at A^{600} of 0.5, at which point they were rapidly heated to 42°C. The flasks were allowed to continue shaking at for three hours.

[0121] Other prokaryotic or eukaryotic host cells may also be used, such as other bacterial cells, strains or species, mammalian cells in culture (COS, CHO or other types) insect cells or multicellular organs or organisms, or plant cells or multicellular organs or organisms, and a skilled practitioner will recognize the appropriate host. The present G-CSF analogs and related compositions may also be prepared synthetically, as, for example, by solid phase peptide synthesis methds, or other chemical manufacturing techniques. Other cloning and expression systems will be apparent to those skilled in the art.

F. Purification of G-CSF Analog Protein

[0122] Cells were harvested by centrifugation (10,000 x G, 20 minutes, 4°C). The pellet (usually 5 grams) was resuspended in 30 ml of 1mM DTT and passed three times through a French press cell at 10,000 psi. The broken cell suspension was centrifuged at 10,000g for 30 minutes, the supernatant removed, and the pellet resuspended in 30-40 ml water. This was recentrifuged at 10,000 x G for 30 minutes, and this pellet was dissolved in 25 ml of 2% Sarkosyl and 50mM Tris at pH 8. Copper sulfate was added to a concentration of 40uM, and the mixture was allowed to stir for at least 15 hours at 15-25°C. The mixture was then centrifuged at 20,000 x G for 30 minutes. The resultant solubilized protein mixture was diluted four-fold with 13.3 mM Tris, pH 7.7, the Sarkosyl was removed, and the supernatant was then applied to a DEAE-cellulose (Whatman DE-52) column equilibrated in 20mM Tris, pH 7.7. After loading and washing the column with the same buffer, the analogs were eluted with 20mM Tris /NaCl (between 35mM to 100mM depending on the analog, as indicated below), pH 7.7. For most of the analogs, the eluent from the DEAE column was adjusted to a pH of 5.4, with 50% acetic acid and diluted as necessary (to obtain the proper conductivity) with 5mM sodium acetate pH 5.4. The solution was then loaded onto a CM-sepharose column equilibrated in 20 mM sodium acetate, pH 5.4. The column was then washed with 20mM NaAc, pH 5.4 until the absorbance at 280 nm was approximately zero. The G-CSF analog was then eluted with sodium acetate/NaCl in concentrations as described below in Table 4. The DEAE column eluents for those analogs not applied to the CM-sepharose column were dialyzed directly into 10mM NaAc, ph 4.0 buffer. The purified G-CSF analogs were then suitably isolated for in vitro analysis. The salt concentrations used for eluting the analogs varied, as noted above. Below, the salt concentrations for the DEAE cellulose column and for the CM-sepharose column are listed:

Table 4

Salt Concentrations

Analog	DEAE Cellulose	CM-Sepharose
Lys^{17}->Arg^{17}	35mM	37.5mM
Lys^{24}->Arg^{24}	35mM	37.5mM
Lys^{35}->Arg^{35}	35mM	37.5mM
Lys^{41}->Arg^{41}	35mM	37.5mM
$Lys^{17,24,35}$->$Arg^{17,24,35}$	35mM	37.5mM
$Lys^{17,35,41}$->$Arg^{17,35,41}$	35mM	37.5mM

Table 4 Con't

Analog	DEAE Cellulose	CM-Sepharose
$Lys^{24,35,41}$->$Arg^{24,35,41}$	35mM	37.5mM
$Lys^{17,24,35,41}$->$Arg^{17,24,35,41}$	35mM	37.5mM
$Lys^{17,24,41}$->$Arg^{17,24,41}$	35mM	37.5mM
Gln^{68}->Glu^{68}	60mM	37.5mM
$Cys^{37,43}$->$Ser^{37,43}$	40mM	37.5mM
Gln^{26}->Ala^{26}	40mM	40mM
Gln^{174}->Ala^{174}	40mM	40mM
Arg^{170}->Ala^{170}	40mM	40mM
Arg^{167}->Ala^{167}	40mM	40mM
Deletion 167*	N/A	N/A
Lys^{41}->Ala^{41}	160mM	40mM
His^{44}->Lys^{44}	40mM	60mM
Glu^{47}->Ala^{47}	40mM	40mM
Arg^{23}->Ala^{23}	40mM	40mM
Lys^{24}->Ala^{24}	120mM	40mM
Glu^{20}->Ala^{20}	40mM	60mM
Asp^{28}->Ala^{28}	40mM	80mM
Met^{127}->Glu^{127}	80mM	40mM
Met^{138}->Glu^{138}	80mM	40mM
Met^{127}->Leu^{127}	40mM	40mM
Met^{138}->Leu^{138}	40mM	40mM
Cys^{18}->Ala^{18}	40mM	37.5mM
$Gln^{12,21}$->$Glu^{12,21}$	60mM	37.5mM
$Gln^{12,21,68}$->$Glu^{12,21,68}$ Glu^{20}->Ala^{20}; Ser^{13}->Gly^{13}	40mM	80mM

Table 4 Con't

Analog	DEAE Cellulose	CM-Sepharose
$Met^{127,138}$->$Leu^{127,138}$	40mM	40mM
Ser^{13}->Ala^{13}	40mM	40mM
Lys^{17}->Ala^{17}	80mM	40mM
Gln^{121}->Ala^{121}	40mM	60mM
Gln^{21}->Ala^{21}	50mM	Gradient 0 -150mM
His^{44}->Ala^{44}**	40mM	N/A
His^{53}->Ala^{53}**	50mM	N/A
Asp^{110}->Ala^{110}**	40mM	N/A
Asp^{113}->Ala^{113}**	40mM	N/A
Thr^{117}->Ala^{117}**	50mM	N/A
Asp^{28}->Ala^{28}; Asp^{110} Ala^{110}**	50mM	N/A
Glu^{124}->Ala^{124}**	40mM	40mM

* For Deletion ^{167}, the data are unavailable.
** For these analogs, the DEAE cellulose column alone was use for purification.

[0123] The above purification methods are illustrative, and a skilled practitioner will recognize that other means are available for obtaining the present G-CSF analogs.

G. Biological Assays

[0124] Regardless of which methods were used to create the present G-CSF analogs, the analogs were subject to assays for biological activity. Tritiated thymidine assays were conducted to ascertain the degree of cell division. Other biological assays, however, may be used to ascertain the desired activity. Biological assays such as assaying for the ability to induce terminal differentiation in mouse WEHI-3B (D+) leukemic cell line, also provides indication of G-CSF activity. See Nicola, et al., Blood 54: 614-27 (1979). Other in vitro assays may be used to ascertain biological activity. See Nicola, Annu. Rev. Biochem. 58: 45-77 (1989). In general, the test for biological activity should provide analysis for the desired result, such as increase or decrease in biological activity (as compared to non-altered G-CSF), different biological activity (as compared to non-altered G-CSF), receptor affinity analysis, or serum half-life analysis. The list is incomplete, and those skilled in the art will recognize other assays useful for testing for the desired end result.

[0125] The ^{3}H-thymidine assay was performed using standard methods. Bone marrow was obtained from sacrificed female Balb C mice. Bone marrow cells were briefly suspended, centrifuged, and resuspended in a growth medium. A 160 ul aliquot containing approximately 10,000 cells was placed into each well of a 96 well micro-titer plate. Samples of the purified G-CSF analog(as prepared above) were added to each well, and incubated for 68 hours. Tritiated thymidine was added to the wells and allowed to incubate for 5 additional hours. After the 5 hour incubation time, the cells were harvested, filtered, and thoroughly rinsed. The filters were added to a vial containing scintillation fluid. The beta emissions were counted (LKB Betaplate scintillation counter). Standards and analogs were analyzed in triplicate, and samples which fell substantially above or below the standard curve were re-assayed with the proper dilution.

The results reported here are the average of the triplicate analog data relative to the unaltered recombinant human G-CSF standard results.

H. HPLC Analysis

[0126] High pressure liquid chromatography was performed on purified samples of analog. Although peak position on a reverse phase HPLC column is not a definitive indication of structural similarity between two proteins, analogs which have similar retention times may have the same type of hydrophobic interactions with the HPLC column as the non-altered molecule. This is one indication of an overall similar structure.

[0127] Samples of the analog and the non-altered recombinant human G-CSF were analyzed on a reverse phase (0.46 x 25 cm) Vydac 214TP54 column (Separations Group, Inc. Hesperia, CA). The purified analog G-CSF samples were prepared in 20 mM acetate and 40 mM NaCl solution buffered at pH 5.2 to a final concentration of 0.1 mg/ml to 5 mg/ml, depending on how the analog performed in the column. Varying amounts (depending on the concentration) were loaded onto the HPLC column, which had been equilibrated with an aqueous solution containing 1% isopropanol, 52.8% acetonitrile, and .38% trifluoro acetate (TFA). The samples were subjected to a gradient of 0.86%/minute acetonitrile, and .002% TFA.

I. Results

[0128] Presented below are the results of the above biological assays and HPLC analysis. Biological activity is the average of triplicate data and reported as a percentage of the control standard (non-altered G-CSF). Relative HPLC peak position is the position of the analog G-CSF relative to the control standard (non-altered G-CSF) peak. The "+" or "-" symbols indicate whether the analog HPLC peak was in advance of or followed the control standard peak (in minutes). Not all of the variants had been analyzed for relative HPLC peak, and only those so analyzed are included below. Also presented are the American Type Culture Collection designations for E. coli host cells containing the nucleic acids coding for the present analogs, as prepared above.

Table 5

Seq. ID	Variant	Analog	Relative HPLC Peak	ATCC No.	% Normal G-CSF Activity
67	1	Lys^{17}->Arg^{17}	N/A	69184	N/A
68	2	Lys^{24}->Arg^{24}	N/A	69185	N/A
69	3	Lys^{35}->Arg^{35}	N/A	69186	N/A
70	4	Lys^{41}->Arg^{41}	N/A	69187	N/A
71	5	$Lys^{17,24,35}$->$Arg^{17,24,35}$	N/A	69189	N/A
72	6	$Lys^{17,35,41}$->$Arg^{17,35,41}$	N/A	69192	N/A
73	7	$Lys^{24,35,41}$->$Arg^{24,35,41}$	N/A	69191	N/A
74	8	$Lys^{17,24,35,41}$ ->$Arg^{17,24,35,41}$	N/A	69193	N/A
75	9	$Lys^{17,24,41}$->$Arg^{17,24,41}$	N/A	69190	N/A
76	10	Gln^{68}->Glu^{68}	N/A	69196	N/A
77	11	$Cys^{37,43}$->$Ser^{37,43}$	N/A	69197	N/A
78	12	Gln^{26}->Ala^{26}	+.96	69201	51%
79	13	Gln^{174}->Ala^{174}	+.14	69202	100%
80	14	Arg^{170}->Ala^{170}	+.78	69203	100%

EP 0 612 846 B1

Table 5 Con't

Seq. ID	Variant	Analog	Relative HPLC Peak	ATCC No.	% Normal G-CSF Activity
81	15	Arg^{167}->Ala^{167}	+.54	69204	110%
82	16	Deletion 167	-.99	69207	N/A
83	17	Lys^{41}->Ala^{41}	+.25	69208	81%
84	18	His^{44}->Lys^{44}	-1.53	69212	70%
85	19	Glu^{47}->Ala^{47}	+.14	69205	0%
86	20	Arg^{23}->Ala^{23}	-.03	69206	31%
87	21	Lys^{24}->Ala^{24}	+1.95	69213	0%
88	22	Glu^{20}->Ala^{20}	-0.07	69211	0%
89	23	Asp^{28}->Ala^{28}	-.30	69210	147%
90	24	Met^{127}->Glu^{127}	N/A	69223	N/A
91	25	Met^{138}->Glu^{138}	N/A	69222	N/A
92	26	Met^{127}->Leu^{127}	N/A	69198	N/A
93	27	Met^{138}->Leu^{138}	N/A	69199	N/A
94	28	Cys^{18}->Ala^{18}	N/A	69188	N/A
95	29	$Gln^{12,21}$->$Glu^{12,21}$	N/A	69194	N/A
96	30	$Gln^{12,21,68}$->$Glu^{12,21,68}$	N/A	69195	N/A
97	31	Glu^{20}->Ala^{20}; Ser^{13}	+1.74	69209	0%

EP 0 612 846 B1

Table 5 Con't

Seq. ID	Variant	Analog	Relative HPLC Peak	ATCC No.	% Normal G-CSF Activity
		->Gly^{13}			
98	32	$Met^{127,138}$->$Leu^{127,138}$	+1.43	69200	98%
99	33	Ser^{13}->Ala^{13}	0	69221	110%
100	34	Lys^{17}->Ala^{17}	+.50	69226	70%
101	35	Gln^{121}->Ala^{121}	+2.7	69225	100%
102	36	Gln^{21}->Ala^{21}	+0.63	69217	9.6%
103	37	His^{44}->Ala^{44}	+1.52	69215	10.8%
104	38	His^{53}->Ala^{53}	+0.99	69219	8.3%
105	39	Asp^{110}->Ala^{110}	+1.97	69216	29%
106	40	Asp^{113}->Ala^{113}	-0.34	69218	0%
107	41	Thr^{117}->Ala^{117}	+0.4	69214	9.7%
108	42	Asp^{28}->Ala^{28}; Asp^{110} Ala^{110}	+3.2	69220	20.6%

Table 5 Con't

Seq. ID	Variant	Analog	Relative HPLC Peak	ATCC No.	% Normal G-CSF Activity
109	43	Glu^{124}->Ala^{124}	+0.16	69224	75%
110	44	Phe^{114}->Val 114, T^{117}->A^{117}**	+0.53		0%

**This analog was apparently a result of an inadvertent error in the oligo which was used to prepare number 41, above (Thr^{117}->Ala 117), and thus was prepared identically to the process used for that analog.

"N/A" indicates data which are not available.

1. Identification of Structure-Function Relationships

[0129] The first step used to design the present analogs was to determine what moieties are necessary for structural integrity of the G-CSF molecule. This was done at the amino acid residue level, although the atomic level is also available for analysis. Modification of the residues necessary for structural integrity results in change in the overall structure of the G-CSF molecule. This may or may not be desirable, depending on the analog one wishes to produce. The working examples here were designed to maintain the overall structural integrity of the G-CSF molecule, for the purpose of maintain G-CSF receptor binding of the analog to the G-CSF receptor (as used in this section below, the "G-CSF receptor" refers to the natural G-CSF receptor, found on hematopoietic cells). It was assumed, and confirmed by the studies presented here, that G-CSF receptor binding is a necessary step for at least one biological activity, as determined by the above biological assays.

[0130] As can be seen from the figures, G-CSF (here, recombinant human met-G-CSF) is an antiparallel 4-alpha helical bundle with a left-handed twist, and with overall dimensions of 45 Å x 30Å x 24Å. The four helices within the bundle are referred to as helices A, B, C and D, and their connecting loops are known as the AB, BC and CD loops. The helix crossing angles range from -167.5° to -159.4°. Helices A, B, and C are straight, whereas helix D contains two kinds of structural characteristics, at Gly 150 and Ser 160 (of the recombinant human met-G-CSF). Overall, the G-CSF molecules is a bundle of four helices, connected in series by external loops. This structural information was then correlated with known functional information. It was known that residues (including methionine at position 1) 47, 23, 24, 20, 21, 44, 53, 113, 110, 28 and 114 may be modified, and the effect on biological activity would be substantial.

[0131] The majority of single mutations which lowered biological activity were centered around two regions of G-CSF that are separated by 30Å, and are located on different faces of the four helix bundle. One region involves interactions between the A helix and the D helix. This is further confirmed by the presence of salt bridges in the non-altered molecule as follows:

Atom	Helix	Atom	Helix	Distance
Arg 170 N1	D	Tyr 166 OH	A	3.3
Tyr 166 OH	D	Arg 23 N2	A	3.3
Glu 163 OE1	D	Arg 23 N1	A	2.8
Arg 23 N1	A	Gln 26 OE1	A	3.1
Gln 159 NE2	D	Gln 26 O	A	3.3

[0132] Distances reported here were for molecule A, as indicated in FIGURE 5 (wherein three G-CSF molecules crystallized together and were designated as A, B, and C). As can be seen, there is a web of salt bridges between helix A and helix D, which act to stabilize the helix A structure, and therefore affect the overall structure of the G-CSF molecule.

[0133] The area centering around residues Glu 20, Arg 23 and Lys 24 are found on the hydrophilic face of the A helix (residues 20-37). Substitution of the residues with the non-charged alanine residue at positions 20 and 23 resulted in similar HPLC retention times, indicating similarity in structure. Alteration of these sites altered the biological activity (as indicated by the present assays). Substitution at Lys 24 altered biological activity, but did not result in a similar HPLC retention time as the other two alterations.

[0134] The second site at which alteration lowered biological activity involves the AB helix. Changing glutamine at position 47 to alanine (analog no. 19, above) reduced biological activity (in the thymidine uptake assay) to zero. The AB helix is predominantly hydrophobic, except at the amino and carboxy termini; it contains one turn of a 3^{10} helix. There are two histadines at each termini (His 44 and His 56) and an additional glutamate at residue 46 which has the potential to form a salt bridge to His 44. The fourier transformed infra red spectrographic analysis (FTIR) of the analog suggests this analog is structurally similar to the non-altered recombinant G-CSF molecule. Further testing showed that this analog would not crystallize under the same conditions as the non-altered recombinant molecule.

[0135] Alterations at the carboxy terminus (Gln 174, Arg 167 and Arg 170) had little effect on biological activity. In contrast, deletion of the last eight residues (167-175) lowered biological activity. These results may indicate that the deletion destabilizes the overall structure which prevents the mutant from proper binding to the G-CSF receptor (and thus initiating signal transduction).

[0136] Generally, for the G-CSF internal core -- the internal four helix bundle lacking the external loops --the hydrophobic internal residues are essential for structural integrity. For example, in helix A, the internal hydrophobic residues

are (with methionine being position 1) Phe 14, Cys 18, Val 22, Ile 25, Ile 32 and Leu 36. Generally, for the G-CSF internal core -- the internal four helix bundle lacking the external loops --the hydrophobic internal residues are essential for structural integrity. For example, in helix A, the internal hydrophobic residues are (with methionine being position 1 as in FIGURE 1) Phe 14, Cys 18, Val 22, Ile 25, Ile 32 and Leu 36. The other hydrophobic residues (again with the met at position 1) are: helix B, Ala 72, Leu 76, Leu 79, Leu 83, Tyr 86, Leu 90 Leu 93; helix C, Leu 104, Leu 107, Val 111, Ala 114, Ile 118, Met 122; and helix D, Val 154, Val 158, Phe 161, Val 164, Val 168, Leu 172.

[0137] The above biological activity data, from the presently prepared G-CSF analogs, demonstrate that modification of the external loops interfere least with G-CSF overall structure. Preferred loops for analog prepration are the AB loop and the CD loop. The loops are relatively flexible structures as compared to the helices. The loops may contribute to the proteolysis of the molecule. G-CSF is relatively fast acting in vivo as the purpose the molecule serves is to generate a response to a biological challenge, i.e., selectively stimulate neutrophils. The G-CSF turnover rate is also relatively fast. The flexibility of the loops may provide a "handle" for proteases to attach to the molecule to inactivate the molecule. Modification of the loops to prevent protease degradation, yet have (via retention of the overall structure of non-modified G-CSF) no loss in biological activity may be accomplished.

[0138] This phenomenon is probably not limited to the G-CSF molecule but may also be common to the other molecules with known similar overall structures, as presented in Figure 2. Alteration of the external loop of, for example hGH, Interferon B, IL-2, GM-CSF and IL-4 may provide the least change to the overall structure. The external loops on the GM-CSF molecule are not as flexible as those found on the G-CSF molecule, and this may indicate a longer serum life, consistent with the broader biological activity of GM-CSF. Thus, the external loops of GM-CSF may be modified by releasing the external loops from the beta-sheet structure, which may make the loops more flexible (similar to those G-CSF) and therefore make the molecule more susceptible to protease degradation (and thus increase the turnover rate).

[0139] Alteration of these external loops may be effected by stabilizing the loops by connection to one or more of the internal helices. Connecting means are known to those in the art, such as the formation of a beta sheet, salt bridge, disulfide bonding or hydrophobic interactions, and other means are available. Also, deletion of one or more moieties, such as one or more amino acid residues or portions thereof, to prepare an abbreviated molecule and thus eliminate certain portions of the external loops may be effected.

[0140] Thus, by alteration of the external loops, preferably the AB loop (amino acids 58-72 of r-hu-met G-CSF) or the CD loop (amino acids 119 to 145 of r-hu-met-G-CSF), and less preferably the amino terminus (amino acids 1-10), one may therefore modify the biological function without elimination of G-CSF receptor binding. For example, one may: (1) increase half-life (or prepare an oral dosage form, for example) of the G-CSF molecule by, for example, decreasing the ability of proteases to act on the G-CSF molecule or adding chemical modifications to the G-CSF molecule, such as one or more polyethylene glycol molecules or enteric coatings for oral formulation which would act to change some characteristic of the G-CSF molecule as described above, such as increasing serum or other half-life or decreasing antigenicity; (2) prepare a hybrid molecule, such as combining G-CSF with part or all of another protein such as another cytokine or another protein which effects signal transduction via entry through the cell through a G-CSF receptor transport mechanism; or (3) increase the biological activity as in, for example, the ability to selectively stimulate neutrophils (as compared to a non-modified G-CSF molecule). This list is not limited to the above exemplars.

[0141] Another aspect observed from the above data is that stabilizing surface interactions may affect biological activity. This is apparent from comparing analogs 23 and 40. Analog 23 contains a substitution of the charged asparagine residue at position 28 for the neutrally-charged alanine residue in that position, and such substitution resulted in a 50% increase in the biological activity (as measured by the disclosed thymidine uptake assays). The asparagine residue at position 28 has a surface interaction with the asparagine residue at position 113; both residues being negatively charged, there is a certain amount of instability (due to the repelling of like charged moieties). When, however the asparagine at position 113 is replaced with the neutrally-charged alanine, the biological activity drops to zero (in the present assay system). This indicates that the asparagine at position 113 is critical to biological activity, and elimination of the asparagine at position 28 serves to increase the effect that asparagine at position 113 possesses.

[0142] The domains required for G-CSF receptor binding were also determined based on the above analogs prepared and the G-CSF structure. The G-CSF receptor binding domain is located at residues (with methionine being position 1) 11-57 (between the A and AB helix) and 100-118 (between the B and C helices). One may also prepare abbreviated molecules capable of binding to a G-CSF receptor and initiate signal transduction for selectively stimulating neutrophils by changing the external loop structure and having the receptor binding domains remain intact.

[0143] Residues essential for biological activity and presumably G-CSF receptor binding or signal transduction have been identified. Two distinct sites are located on two different regions of the secondary structure. What is here called "Site A" is located on a helix which is constrained by salt bridge contacts between two other members of the helical bundle. The second site, "Site B" is located on a relatively more flexible helix, AB. The AB helix is potentially more sensitive to local pH changes because of the type and position of the residues at the carboxy and amino termini. The functional importance of this flexible helix may be important in a conformationally induced fit when binding to the G-CSF receptor. Additionally, the extended portion of the D helix is also indicated to be a G-CSF receptor binding domain, as

ascertained by direct mutational and indirect comparative protein structure analysis. Deletion of the carboxy terminal end of r-hu-met-G-CSF reduces activity as it does for hGH, see, Cunningham and Wells, Science 244: 1081-1084 (1989). Cytokines which have similar structures, such as IL-6 and GM-CSF with predicted similar topology also center their biological activity along the carboxy end of the D helix, see Bazan, Immunology Today 11: 350-354 (1990)

[0144] A comparison of the structures and the positions of G-CSF receptor binding determinants between G-CSF and hGH suggests both molecules have similar means of signal transduction. Two separate G-CSF receptor binding sites have been identified for hGH De Vos et al., Science 255: 306-32 (1991). One of these binding sites (called "Site I") is formed by residues on the exposed faces of hGH's helix 1, the connection region between helix 1 and 2, and helix 4. The second binding site (called "Site II") is formed by surface residues of helix 1 and helix 3.

[0145] The G-CSF receptor binding determinates identified for G-CSF are located in the same relative positions as those identified for hGH. The G-CSF receptor binding site located in the connecting region between helix A and B on the AB helix (Site A) is similar in position to that reported for a small piece of helix (residues 38-47) of hGH. A single point mutation in the AB helix of G-CSF significantly reduces biological activity (as ascertained in the present assays), indicating the role in a G-CSF receptor-ligand interface. Binding of the G-CSF receptor may destabilize the 3^{10} helical nature of this region and induce a conformation change improving the binding energy of the ligand/G-CSF receptor complex.

[0146] In the hGH receptor complex, the first helix of the bundle donates residues to both of the binding sites required to dimerize the hGH receptor Mutational analysis of the corresponding helix of G-CSF (helix A) has identified three residues which are required for biological activity. Of these three residues, Glu 20 and Arg 24 lie on one face of the helical bundle towards helix C, whereas the side chain of Arg 23 (in two of the three molecules in the asymmetric unit) points to the face of the bundle towards helix D. The position of side chains of these biologically important residues indicates that similar to hGH, G-CSF may have a second G-CSF receptor binding site along the interface between helix A and helix C. In contrast with the hGH molecule, the amino terminus of G-CSF has a limited biological role as deletion of the first 11 residues has little effect on the biological activity.

[0147] As indicated above (see FIGURE 2, for example), G-CSF has a topological similarity with other cytokines. A correlation of the structure with previous biochemical studies, mutational analysis and direct comparison of specific residues of the hGH receptor complex indicates that G-CSF has two receptor binding sites. Site A lies along the interface of the A and D helices and includes residues in the small AB helix. Site B also includes residues in the A helix but lies along the interface between helices A and C. The conservation of structure and relative positions of biologically important residues between G-CSF and hGH is one indication of a common method of signal transduction in that the receptor is bound in two places. It is therefore found that G-CSF analogs possessing altered G-CSF receptor binding domains may be prepared by alteration at either of the G-CSF receptor binding sites (residues 20-57 and 145-175).

[0148] Knowledge of the three dimensional structure and correlation of the composition of G-CSF protein makes possible a systematic, rational method for preparing G-CSF analogs. The above working examples have demonstrated that the limitations of the size and polarity of the side chains within the core of the structure dictate how much change the molecule can tolerate before the overall structure is changed.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Amgen Inc.

(ii) TITLE OF INVENTION: G-CSF ANALOG COMPOSITIONS AND METHODS

(iii) NUMBER OF SEQUENCES: 110

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Amgen Inc.
(B) STREET: Amgen Center, 1840 DeHavilland Drive
(C) CITY: Thousand Oaks
(D) STATE: California
(E) COUNTRY: United States of America
(F) ZIP: 91320-1789

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 565 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 30..554

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

```
TCTAGAAAAA ACCAAGGAGG TAATAAATA ATG ACT CCA TTA GGT CCT GCT TCT          53
                                Met Thr Pro Leu Gly Pro Ala Ser
                                  1               5

TCT CTG CCG CAA AGC TTT CTG CTG AAA TGT CTG GAA CAG GTT CGT AAA          101
Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys
    10                  15                  20

ATC CAG GGT GAC GGT GCT GCA CTG CAA GAA AAA CTG TGC GCT ACT TAC          149
Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr
 25                  30                  35                  40
```

```
AAA CTG TGC CAT CCG GAA GAG CTG GTA CTG CTG GGT CAT TCT CTT GGG      197
Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly
                45                  50                  55

ATC CCG TGG GCT CCG CTG TCT TCT TGT CCA TCT CAA GCT CTT CAG CTG      245
Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu
            60                  65                  70

GCT GGT TGT CTG TCT CAA CTG CAT TCT GGT CTG TTC CTG TAT CAG GGT      293
Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly
        75                  80                  85

CTT CTG CAA GCT CTG GAA GGT ATC TCT CCG GAA CTG GGT CCG ACT CTG      341
Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu
    90                  95                  100

GAC ACT CTG CAG CTA GAT GTA GCT GAC TTT GCT ACT ACT ATT TGG CAA      389
Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln
105                 110                 115                 120

CAG ATG GAA GAG CTC GGT ATG GCA CCA GCT CTG CAA CCG ACT CAA GGT      437
Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly
            125                 130                 135

GCT ATG CCG GCA TTC GCT TCT GCA TTC CAG CGT CGT GCA GGA GGT GTA      485
Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val
        140                 145                 150

CTG GTT GCT TCT CAT CTG CAA TCT TTC CTG GAA GTA TCT TAC CGT GTT      533
Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val
    155                 160                 165

CTG CGT CAT CTG GCT CAG CCG TAATAGAATT C                             565
Leu Arg His Leu Ala Gln Pro
170                 175
```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45
```

```
Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
 50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CATTCTGCTG CGTTGTCTGG AACA 24

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

ACAGGTTCGT CGTATCCAGG GTG 23

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CACTGCAAGA ACGTCTGTGC GCT 23

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

CGCTACTTAC CGTCTGTGCC ATC 23

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CTTTCTGCTG CGTTGTCTGG AACA 24

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

ACAGGTTCGT CGTATCCAGG GTG 23

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

CTGCAAGA ACGTCTGTGC GCT 23

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

CTTTCTGCTG CGTTGTCTGG AACA 24

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

ACAGGTTCGT CGTATCCAGG GTG 23

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

CGCTACTTAC CGTCTGTCCC ATC 23

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

CTTTCTGCTG CGTTGTCTGG AACA 24

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

TTGCAAGA ACGTCTGTGC GCT 23

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

CGCTACTTAC CGTCTGTGCC ATC 23

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

ACAGGTTCGT CGTATCCAGG GTG 23

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

CACTGCAAGA ACGTCTGTGC GCT 23

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

CGCTACTTAC CGTCTGTGCC ATC 23

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

CTTTCTGCTG CGTTGTCTGG AACA 24

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

AGGTTCGT CGTATCCAGG GTG 23

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

CACTGCAAGA ACGTCTGTGC GCT 23

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

CGCTACTTAC CGTCTGTGCC ATC 23

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

TCTGCTGAAA GCTCTGGAAC AGG 23

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

CTTGTCCATC TGAAGCTCTT CAG 23

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

[illegible]AAACTGT CCGCTACTTA CAAACTGTCC CATCCGG 37

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

TTCGTAAAAT CGCGGGTGAC GG 22

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

TCATCTGGCT GCGCCGTAAT AG 22

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

CCGTGTTCTG GCTCATCTGG CT 22

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GAAGTATCTT ACGCTGTTCT GCGT 24

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

GAAGTATCTT ACTAAGTTCT GCGTC 25

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

CTACTTAC GCACTGTGCC AT 22

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

CAAACTGTGC AAGCCGGAAG AG 22

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

CATCCGGAAG CACTGGTACT GC 22

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

GGAACAGGTT GCTAAAATCC AGG 23

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

GAACAGGTTC GTGCGATCCA GGGTG 25

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

AATGTCTG GCACAGGTTC GT 22

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

TCCAGGGTGC CGGTGCTGC 19

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

AAGAGCTCGG TGAGGCACCA GCT 23

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

CTCAAGGTGC TGAGCCGGCA TTC 23

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

GAGCTCGGTC TGGCACCAGC 20

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

TCAAGGTGCT CTGCCGGCAT T 21

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

TGCCGCAA GCCTTTCTGC TGA 23

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

CTTTCTGCTG GCATGTCTGG AACA 24

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

CTATTTGGCA AGCGATGGAA GAGC 24

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

CAGATGGAAG CGCTCGGTAT G 21

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

GAGCTCGGTC TGGCACCAGC 20

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

AAGGTGCT CTGCCGGCAT T 21

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

GAAATGTCTG GCACAGGTTC GT 22

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

TTCCGGAGCG CACAGTTTG 19

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

CGAGAAGGCC TCGGGTGTCA AAC 23

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

ATGCCAAATT GCAGTAGCAA AG 22

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

ACAACGGTTT AACGTCATCG TTTC 24

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

TCAGCTACT GCTAGCTGCA GA 22

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

TCAGTCGATG ACGATCGACG TCT 23

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

TTACGAACCG CTTCCAGACA TT 22

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

TAAAATGCTT GGCGAAGGTC TGTAA 25

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

GTAGCAAATG CAGCTACATC TA 22

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

CTCATCGTT TACGTCGATG TAGAT 25

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

CCAAGAGAAG CACCCAGCAG 20

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

AGGGTTCTCT TCGTGGGTCG TC 22

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

CACTGGCGGT GATAATGAGC 20

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

CTAGGCCAGG CATTACTGG 19

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

CCACTGGCGG TGATACTGAG C 21

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

AGCAGAAAGC TTTCCGGCAG AGAAGAAGCA GGA 33

(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 54 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

GCCGCAAAGC TTTCTGCTGA AATGTCTGGA AGAGGTTCGT AAAATCCAGG GTGA 54

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 59 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

CTGGAATGCA GAAGCAAATG CCGGCATAGC ACCTTCAGTC GGTTGCAGAG CTGGTGCCA 59

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Arg Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Arg Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30
```

```
Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
 35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
 50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                 85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Arg Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95
```

```
Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
                100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Arg Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160
```

```
Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Val Cys Leu Glu Gln Val Arg Arg Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Arg Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Arg Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Arg Leu Cys Ala Thr Tyr Arg Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Arg Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Arg Leu Cys Ala Thr Tyr Arg Leu Cys His Pro Glu Glu Leu
        35                  40                  45
```

```
Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
     50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                 85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Ile Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Arg Cys Leu Glu Gln Val Arg Arg Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Arg Leu Cys Ala Thr Tyr Arg Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110
```

```
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
  1               5                  10                  15

Arg Cys Leu Glu Gln Val Arg Arg Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Arg Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15
Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Glu Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Leu Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Ser Ala Thr Tyr Lys Leu Ser His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

. r Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Ala Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60
```

```
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

...e Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
  1               5                  10                  15

*-*s Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125
```

```
Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Ala Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
  1                 5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Ala His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Ala Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 174 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Xaa Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Val Leu Arg His Leu Ala Gln Pro
                165                 170                 174
```

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Ala Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60
```

```
Cys Pro Ser Gln Ala Leu Gln L u Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                 85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

...e Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
  1               5                  10                  15

T s Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys Lys Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125
```

```
Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
  1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Ala Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Ala Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Ala Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Ala Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60
```

```
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Ile Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Ala Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125
```

```
Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
  1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Glu Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Glu Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Leu Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60
```

```
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Leu Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

  e Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
  1               5                  10                  15

  s Ala Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125
```

```
Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:95:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Glu Ser Phe Leu Leu
  1               5                  10                  15

Lys Cys Leu Glu Glu Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Glu Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Glu Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Glu Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Gly Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Ala Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45
```

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Leu Ala
115 120 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Leu Pro Ala Phe Ala Ser Ala
130 135 140

Leu Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:99:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ala Phe Leu Leu
1 5 10 15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
35 40 45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110

```
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
          115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
      130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                    165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
  1               5                  10                  15

Ala Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
          115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
      130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                    165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:101:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Ala Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:102:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Ala Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:103:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys Ala Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60
```

```
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

...e Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
  1               5                  10                  15

 ...s Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly Ala Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125
```

```
Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:105:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
  1                 5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Gly Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Ala Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:106:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Ala Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:107:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Xaa Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Ala Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:108:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Ala Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60
```

```
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                 85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Ala Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:109:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Xaa Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110
```

```
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Ala Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:110:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Val Ala Thr Ala Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

Claims

1. A method for preparing a G-CSF analog comprising the steps of:

   (a) viewing at the amino acid or atomic level information conveying the three dimensional structure of a G-CSF molecule as set forth in Figure 5;
   (b) selecting from said viewed information at least one site on said G-CSF molecule for alteration;
   (c) preparing a G-CSF molecule having such alteration; and
   (d) optionally, testing such G-CSF molecule for a desired characteristic.

2. A method for preparing a G-CSF analog according to claim 1 based on the use of a computer comprising the steps of:

   (a) providing computer expression at the amino acid or atomic level of the three dimensional structure of a G-CSF molecule as set forth in Figure 5;
   (b) selecting from said computer expression at least one site on said G-CSF molecule for alteration;
   (c) preparing a G-CSF molecule having such alteration; and,
   (d) optionally, testing such G-CSF molecule for a desired characteristic.

3. A method for preparing a G-CSF analog according to claim 2 comprising:

   (a) providing said computer with the means for displaying the three dimensional structure of a G-CSF molecule as set forth in Figure 5; including displaying the composition of moieties of said G-CSF molecule, preferably displaying the three dimensional location of each amino acid, and more preferably displaying the three dimensional location of each atom of a G-CSF molecule;
   (b) viewing said display;
   (c) selecting a site on said display for alteration in the composition of said molecule or the location of a moiety; and
   (d) preparing a G-CSF analog with such alteration.

4. A computer-based method for preparing a G-CSF analog comprising the steps of:

   (a) viewing at the amino acid or atomic level the three dimensional structure of a G-CSF molecule as set forth in Figure 5; via a computer, said computer having been previously programmed (i) to express the coordinates of a G-CSF molecule in three dimensional space, and (ii) to allow for entry of information for alteration of said G-CSF expression and viewing thereof;
   (b) selecting a site on said visual image of said G-CSF molecule for alteration;
   (c) entering information for said alteration on said computer;
   (d) viewing a three dimensional structure of said altered G-CSF molecule via said computer;
   (e) optionally repeating steps (a)-(e) above;
   (f) preparing a G-CSF analog with said alteration; and
   (g) optionally testing said G-CSF analog for a desired characteristic.

Patentansprüche

1. Verfahren zur Herstellung eines G-CSF-Analogs, welches die Schritte umfaßt:

   (a) Betrachten, auf dem Aminosäure- oder Atomniveau, von Information, welche die dreidimensionale Struktur eines G-CSF-Moleküls, wie angegeben in Fig. 5, vermittelt;

   (b) Auswählen, aus besagter betrachteten Information, von wenigstens einer Stelle auf besagtem G-CSF-Molekül für eine Veränderung;

   (c) Herstellen eines G-CSF-Moleküls mit einer solchen Veränderung; und

   (d) fakultativ, Testen eines solchen G-CSF-Moleküls auf eine gewünschte Eigenschaft.

2. Verfahren zur Herstellung eines G-CSF-Analogs nach Anspruch 1, auf der Basis der Verwendung eines Compu-

ters, welches die Schritte umfaßt:

(a) Bereitstellen einer Computerdarstellung, auf dem Aminosäure- oder Atomniveau, der dreidimensionalen Struktur eines G-CSF-Moleküls, wie angegeben in Fig. 5;

(b) Auswählen, aus besagter Computerdarstellung, von wenigstens einer Stelle auf besagtem G-CSF-Molekül für eine Veränderung;

(c) Herstellen eines G-CSF-Moleküls mit einer solchen Veränderung; und

(d) fakultativ, Testen eines solchen G-CSF-Moleküls auf eine gewünschte Eigenschaft.

3. Verfahren zur Herstellung eines G-CSF-Analogs nach Anspruch 2, welches umfaßt:

(a) Versehen besagten Computers mit Mitteln zum Anzeigen der dreidimensionalen Struktur eines G-CSF-Moleküls, wie angegeben in Fig. 5, einschließlich Anzeigen der Zusammensetzung der Einheiten besagten G-CSF-Moleküls, vorzugsweise Anzeigen der dreidimensionalen Anordnung jeder Aminosäure und bevorzugter Anzeigen der dreidimensionalen Anordnung jedes Atoms eines G-CSF-Moleküls;

(b) Betrachten besagter Ansicht;

(c) Auswählen einer Stelle auf besagter Ansicht für eine Veränderung in der Zusammensetzung besagten Moleküls oder der Anordnung einer Einheit; und

(d) Herstellen eines G-CSF-Analogs mit solch einer Änderung.

4. Computergestütztes Verfahren zur Herstellung eines G-CSF-Analogs, welches die Schritte umfaßt:

(a) Betrachten, auf dem Aminosäure- oder Atomniveau, der dreidimensionalen Struktur eines G-CSF-Moleküls, wie angegeben in Fig. 5, über einen Computer, wobei besagter Computer zuvor so programmiert worden ist, daß er (i) die Koordinaten eines G-CSF-Moleküls im dreidimensionalen Raum darstellt und (ii) die Eingabe von Information zur Veränderung besagter G-CSF-Darstellung und Betrachtung derselben ermöglicht;

(b) Auswählen einer Stelle auf besagtem visuellen Bild besagten G-CSF-Moleküls für eine Veränderung;

(c) Eingeben der Information für besagte Veränderung in besagten Computer;

(d) Betrachten einer dreidimensionalen Struktur besagten veränderten G-CSF-Moleküls über besagten Computer;

(e) fakultativ, Wiederholen der Schritte (a) - (e) oben;

(f) Herstellen eines G-CSF-Analogs mit besagter Veränderung; und

(g) fakultativ, Testen besagten G-CSF-Analogs auf eine gewünschte Eigenschaft.

Revendications

1. Procédé pour préparer un analogue de G-CSF, comprenant les étapes de :

(a) visualiser au niveau atomique ou des acides aminés des informations fournissant la structure tridimensionnelle d'une molécule de G-CSF comme indiqué sur la figure 5,
(b) choisir à partir desdites informations visualisées au moins un site sur ladite molécule de G-CSF pour altération ;
(c) préparer une molécule de G-CSF ayant une telle altération ; et
(d) éventuellement, tester une telle molécule de G-CSF en ce qui concerne une caractéristique souhaitée.

2. Procédé pour préparer un analogue de G-CSF selon la revendication 1, basé sur l'utilisation d'un ordinateur, com-

prenant les étapes de :

(a) fournir l'expression par ordinateur au niveau atomique ou des acides aminés de la structure tridimensionnelle d'une molécule de G-CSF comme indiqué sur la figure 5,
(b) choisir à partir de ladite expression par ordinateur au moins un site sur ladite molécule de G-CSF pour altération ;
(c) préparer une molécule de G-CSF ayant une telle altération ; et
(d) éventuellement, tester une telle molécule de G-CSF en ce qui concerne une caractéristique souhaitée.

3. Procédé pour préparer un analogue de G-CSF selon la revendication 2, comprenant :

(a) munir ledit ordinateur des moyens pour afficher la structure tridimensionnelle d'une molécule de G-CSF comme indiqué sur la figure 5 incluant l'affichage de la composition des fractions de ladite molécule de G-CSF, en affichant de préférence l'emplacement tridimensionnel de chaque acide aminé, et, plus préférablement, en affichant l'emplacement tridimensionnel de chaque atome d'une molécule de G-CSF ;
(b) visualiser ledit affichage ;
(c) choisir un site sur ledit affichage pour altération de la composition de ladite molécule ou de l'emplacement d'une fraction ; et
(d) préparer un analogue de G-CSF ayant une telle altération.

4. Procédé assisté par ordinateur pour préparer un analogue de G-CSF, comprenant les étapes de :

(a) visualiser au niveau atomique ou des acides aminés la structure tridimensionnelle d'une molécule de G-CSF comme indiqué sur la figure 5 via un ordinateur, ledit ordinateur ayant été préalablement programmé (i) pour exprimer les coordonnées d'une molécule de G-CSF dans l'espace tridimensionnel, et (ii) pour permettre l'entrée des informations pour l'altération de ladite expression de G-CSF et sa visualisation ;
(b) choisir un site sur ladite image visuelle de ladite molécule de G-CSF pour altération ;
(c) entrer des informations pour ladite altération dans ledit ordinateur ;
(d) visualiser une structure tridimensionnelle de ladite molécule de G-CSF altérée via ledit ordinateur ;
(e) répéter éventuellement les étapes (a) - (e) ci-dessus ;
(f) préparer un analogue de G-CSF ayant ladite altération ; et
(g) tester éventuellement ledit analogue de G-CSF en ce qui concerne une caractéristique souhaitée.

```
                                        Met Thr Pro Leu Gly Pro Ala
TCTAGAAAAAACCAAGCAGGTAATAAATA ATG ACT CCA TTA GGT CCT GCT

Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln
TCT TCT CTG CCG CAA AGC TTT CTG CTG AAA TGT CTG GAA CAG

Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu
GTT CGT AAA ATC CAG GGT GAC GGT GCT GCA CTG CAA GAA AAA CTG

Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu
TGC GCT ACT TAC AAA CTG TGC CAT CCG GAA GAG CTG GTA CTG CTG

Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro
GGT CAT TCT CTT GGG ATC CCG TGG GCT CCG CTG TCT TCT TGT CCA

Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser
TCT CAA GCT CTT CAG CTG GCT GGT TGT CTG TCT CAA CTG CAT TCT

Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
GGT CTG TTC CTG TAT CAG GGT CTT CTG CAA GCT CTG GAA GGT ATC

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val
TCT CCG GAA CTG GGT CCG ACT CTG GAC ACT CTG CAG CTA GAT GTA

Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly
GCT GAC TTT GCT ACT ACT ATT TGG CAA CAG ATG GAA GAG CTC GGT

Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe
ATG GCA CCA GCT CTG CAA CCG ACT CAA GGT GCT ATG CCG GCA TTC

Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser
GCT TCT GCA TTC CAG CGT CGT GCA GGA GGT GTA CTG GTT GCT TCT

His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His
CAT CTG CAA TCT TTC CTG GAA GTA TCT TAC CGT GTT CTG CGT CAT

Leu Ala Gln Pro OC  AM
CTG GCT CAG CCG TAA TAG AATTC
```

FIGURE 1

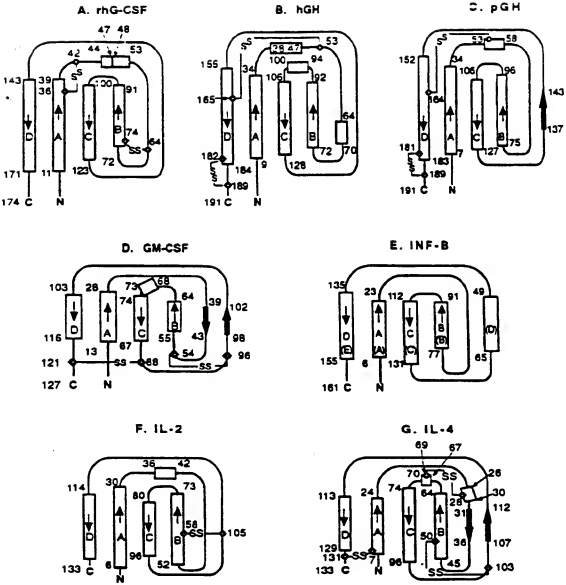


FIGURE 2

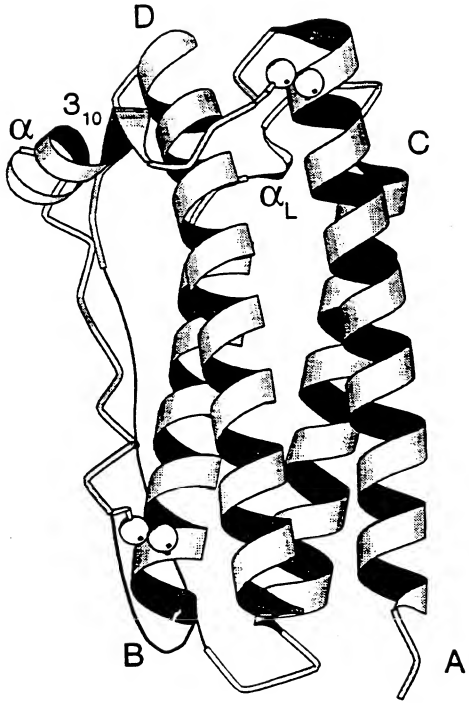


FIGURE 3

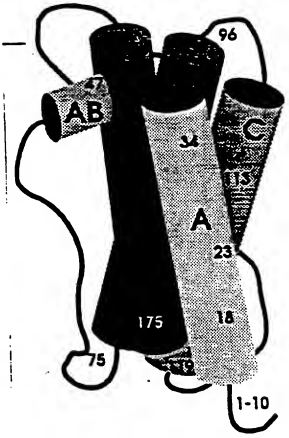
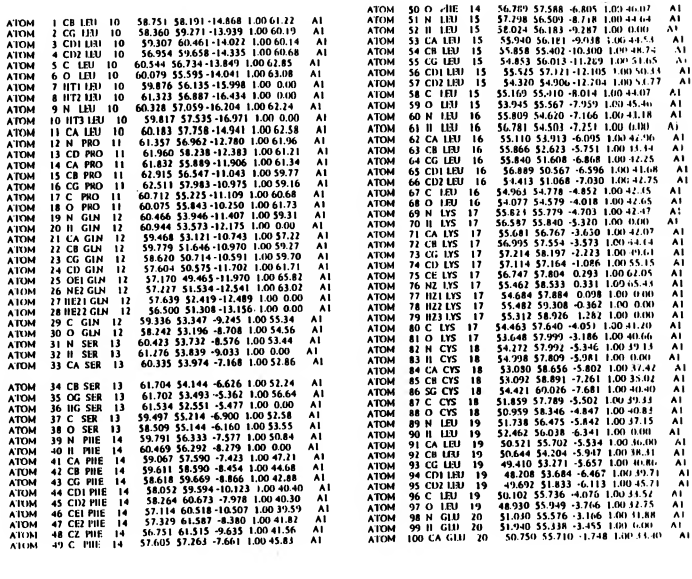


FIGURE 4

FIGURE 5



```
ATOM    1 CB  LEU  10     58.751  58.191 -14.868  1.00 61.22      A1
ATOM    2 CG  LEU  10     58.360  59.271 -13.939  1.00 60.19      A1
ATOM    3 CD1 LEU  10     59.307  60.461 -14.022  1.00 60.14      A1
ATOM    4 CD2 LEU  10     56.954  59.658 -14.335  1.00 60.68      A1
ATOM    5 C   LEU  10     60.544  56.734 -13.849  1.00 62.85      A1
ATOM    6 O   LEU  10     60.079  55.595 -14.041  1.00 63.08      A1
ATOM    7 1HT1 LEU  10     59.876  56.135 -15.998  1.00  0.00      A1
ATOM    8 1HT2 LEU  10     61.323  56.887 -16.434  1.00  0.00      A1
ATOM    9 N   LEU  10     60.328  57.059 -16.204  1.00 62.24      A1
ATOM   10 1HT3 LEU  10     59.817  57.535 -16.971  1.00  0.00      A1
ATOM   11 CA  LEU  10     60.183  57.758 -14.941  1.00 62.58      A1
ATOM   12 N   PRO  11     61.357  56.962 -12.780  1.00 61.96      A1
ATOM   13 CD  PRO  11     61.960  58.238 -12.383  1.00 61.21      A1
ATOM   14 CA  PRO  11     61.832  55.889 -11.906  1.00 61.34      A1
ATOM   15 CB  PRO  11     62.915  56.547 -11.043  1.00 59.77      A1
ATOM   16 CG  PRO  11     62.511  57.983 -10.975  1.00 59.16      A1
ATOM   17 C   PRO  11     60.712  55.225 -11.109  1.00 60.68      A1
ATOM   18 O   PRO  11     60.075  55.843 -10.250  1.00 61.73      A1
ATOM   19 N   GLN  12     60.466  53.946 -11.407  1.00 59.31      A1
ATOM   20 H   GLN  12     60.944  53.573 -12.175  1.00  0.00      A1
ATOM   21 CA  GLN  12     59.468  53.121 -10.743  1.00 57.22      A1
ATOM   22 CB  GLN  12     59.779  51.646 -10.970  1.00 59.27      A1
ATOM   23 CG  GLN  12     58.620  50.714 -10.591  1.00 59.70      A1
ATOM   24 CD  GLN  12     57.604  50.575 -11.702  1.00 61.71      A1
ATOM   25 OE1 GLN  12     57.170  49.465 -11.970  1.00 65.82      A1
ATOM   26 NE2 GLN  12     57.227  51.534 -12.541  1.00 63.02      A1
ATOM   27 HE21 GLN  12     57.639  52.419 -12.489  1.00  0.00      A1
ATOM   28 HE22 GLN  12     56.500  51.308 -13.156  1.00  0.00      A1
ATOM   29 C   GLN  12     59.336  53.347 -9.245  1.00 55.34      A1
ATOM   30 O   GLN  12     58.242  53.196 -8.708  1.00 54.56      A1
ATOM   31 N   SER  13     60.423  53.737 -8.576  1.00 53.44      A1
ATOM   32 H   SER  13     61.276  53.839 -9.033  1.00  0.00      A1
ATOM   33 CA  SER  13     60.335  53.974 -7.168  1.00 52.86      A1

ATOM   34 CB  SER  13     61.704  54.144 -6.626  1.00 52.24      A1
ATOM   35 OG  SER  13     61.702  53.493 -5.362  1.00 56.64      A1
ATOM   36 HG  SER  13     61.534  52.551 -5.477  1.00  0.00      A1
ATOM   37 C   SER  13     59.497  55.214 -6.900  1.00 52.58      A1
ATOM   38 O   SER  13     58.509  55.144 -6.160  1.00 53.55      A1
ATOM   39 N   PHE  14     59.791  56.333 -7.577  1.00 50.84      A1
ATOM   40 H   PHE  14     60.469  56.292 -8.279  1.00  0.00      A1
ATOM   41 CA  PHE  14     59.067  57.590 -7.423  1.00 47.21      A1
ATOM   42 CB  PHE  14     59.611  58.590 -8.454  1.00 44.68      A1
ATOM   43 CG  PHE  14     58.618  59.669 -8.866  1.00 42.88      A1
ATOM   44 CD1 PHE  14     58.052  59.594 -10.123  1.00 40.40      A1
ATOM   45 CD2 PHE  14     58.264  60.673 -7.978  1.00 40.30      A1
ATOM   46 CE1 PHE  14     57.114  60.518 -10.507  1.00 39.59      A1
ATOM   47 CE2 PHE  14     57.329  61.587 -8.380  1.00 41.82      A1
ATOM   48 CZ  PHE  14     56.751  61.515 -9.635  1.00 41.56      A1
ATOM   49 C   PHE  14     57.605  57.263 -7.661  1.00 45.83      A1

ATOM   50 O   PHE  14     56.789  57.588 -6.805  1.00 46.07      A1
ATOM   51 N   LEU  15     57.298  56.509 -8.718  1.00 44.64      A1
ATOM   52 H   LEU  15     58.024  56.183 -9.287  1.00  0.00      A1
ATOM   53 CA  LEU  15     55.940  56.181 -9.038  1.00 44.54      A1
ATOM   54 CB  LEU  15     55.858  55.402 -10.300  1.00 48.75      A1
ATOM   55 CG  LEU  15     54.853  56.013 -11.269  1.00 51.65      A1
ATOM   56 CD1 LEU  15     55.525  57.121 -12.105  1.00 50.33      A1
ATOM   57 CD2 LEU  15     54.320  54.906 -12.004  1.00 51.77      A1
ATOM   58 C   LEU  15     55.169  55.410 -8.014  1.00 44.07      A1
ATOM   59 O   LEU  15     53.945  55.567 -7.959  1.00 45.44      A1
ATOM   60 N   LEU  16     55.809  54.620 -7.166  1.00 43.18      A1
ATOM   61 H   LEU  16     56.781  54.503 -7.251  1.00  0.00      A1
ATOM   62 CA  LEU  16     55.110  53.913 -6.095  1.00 42.96      A1
ATOM   63 CB  LEU  16     55.866  52.623 -5.751  1.00 43.14      A1
ATOM   64 CG  LEU  16     55.840  51.608 -6.868  1.00 42.25      A1
ATOM   65 CD1 LEU  16     56.889  50.567 -6.596  1.00 41.68      A1
ATOM   66 CD2 LEU  16     54.413  51.068 -7.030  1.00 42.75      A1
ATOM   67 C   LEU  16     54.963  54.778 -4.852  1.00 42.15      A1
ATOM   68 O   LEU  16     54.077  54.579 -4.018  1.00 42.65      A1
ATOM   69 N   LYS  17     55.821  55.779 -4.703  1.00 42.47      A1
ATOM   70 H   LYS  17     56.587  55.840 -5.320  1.00  0.00      A1
ATOM   71 CA  LYS  17     55.681  56.767 -3.630  1.00 42.07      A1
ATOM   72 CB  LYS  17     56.995  57.554 -3.573  1.00 44.14      A1
ATOM   73 CG  LYS  17     57.214  58.197 -2.223  1.00 49.61      A1
ATOM   74 CD  LYS  17     57.114  57.164 -1.086  1.00 55.15      A1
ATOM   75 CE  LYS  17     56.747  57.804  0.293  1.00 62.05      A1
ATOM   76 NZ  LYS  17     55.462  58.533  0.331  1.00 64.44      A1
ATOM   77 HZ1 LYS  17     54.684  57.884  0.098  1.00  0.00      A1
ATOM   78 HZ2 LYS  17     55.482  59.308 -0.362  1.00  0.00      A1
ATOM   79 HZ3 LYS  17     55.312  58.926  1.282  1.00  0.00      A1
ATOM   80 C   LYS  17     54.463  57.640 -4.051  1.00 41.20      A1
ATOM   81 O   LYS  17     53.648  57.999 -3.186  1.00 40.66      A1
ATOM   82 N   CYS  18     54.272  57.992 -5.346  1.00 39.13      A1
ATOM   83 H   CYS  18     54.998  57.809 -5.981  1.00  0.00      A1
ATOM   84 CA  CYS  18     53.080  58.656 -5.802  1.00 37.42      A1
ATOM   85 CB  CYS  18     53.092  58.891 -7.261  1.00 35.02      A1
ATOM   86 SG  CYS  18     54.421  60.026 -7.681  1.00 40.40      A1
ATOM   87 C   CYS  18     51.859  57.789 -5.502  1.00 39.33      A1
ATOM   88 O   CYS  18     50.959  58.346 -4.847  1.00 40.84      A1
ATOM   89 N   LEU  19     51.738  56.475 -5.842  1.00 37.15      A1
ATOM   90 H   LEU  19     52.462  56.038 -6.341  1.00  0.00      A1
ATOM   91 CA  LEU  19     50.521  55.702 -5.534  1.00 36.00      A1
ATOM   92 CB  LEU  19     50.644  54.204 -5.947  1.00 38.31      A1
ATOM   93 CG  LEU  19     49.410  53.271 -5.657  1.00 40.86      A1
ATOM   94 CD1 LEU  19     48.208  53.684 -6.467  1.00 39.71      A1
ATOM   95 CD2 LEU  19     49.692  51.833 -6.113  1.00 45.71      A1
ATOM   96 C   LEU  19     50.102  55.736 -4.076  1.00 34.52      A1
ATOM   97 O   LEU  19     48.930  55.949 -3.766  1.00 32.75      A1
ATOM   98 N   GLU  20     51.030  55.576 -3.166  1.00 31.88      A1
ATOM   99 H   GLU  20     51.940  55.338 -3.455  1.00  0.00      A1
ATOM  100 CA  GLU  20     50.750  55.710 -1.748  1.00 31.40      A1
```

FIGURE 5

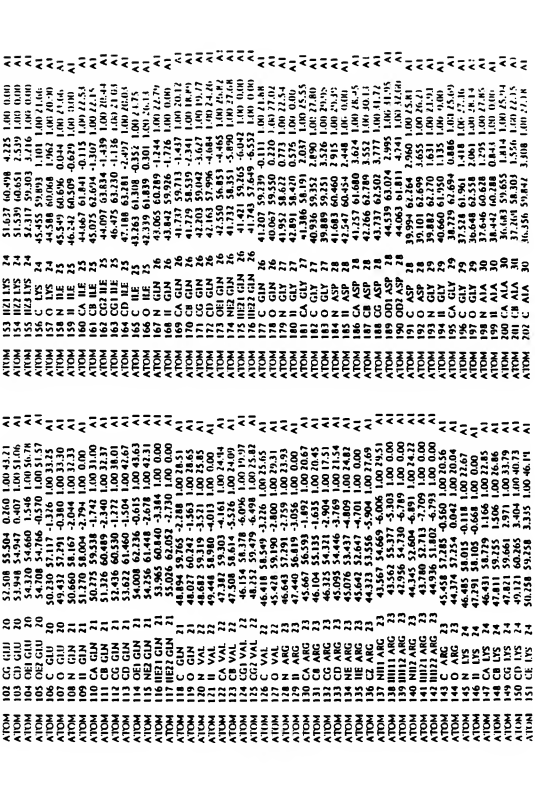


FIGURE 5

```
ATOM  203 O  ALA  30      35.194 59.772  3.754 1.00 28.82      A1
ATOM  204 N  ALA  31      37.340 60.105  4.150 1.00 27.16      A1
ATOM  205 H  ALA  31      38.253 60.114  3.809 1.00  0.00      A1
ATOM  206 CA ALA  31      37.113 60.470  5.531 1.00 27.70      A1
ATOM  207 CB ALA  31      38.383 60.881  6.177 1.00 27.65      A1
ATOM  208 C  ALA  31      36.178 61.675  5.660 1.00 30.01      A1
ATOM  209 O  ALA  31      35.195 61.624  6.413 1.00 32.91      A1
ATOM  210 N  LEU  32      36.397 62.744  4.895 1.00 27.63      A1
ATOM  211 H  LEU  32      37.133 62.734  4.242 1.00  0.00      A1
ATOM  212 CA LEU  32      35.560 63.898  4.997 1.00 28.52      A1
ATOM  213 CB LEU  32      36.226 65.019  4.167 1.00 32.94      A1
ATOM  214 CG LEU  32      35.658 66.472  4.091 1.00 32.54      A1
ATOM  215 CD1 LEU  32     35.516 67.082  5.499 1.00 32.87      A1
ATOM  216 CD2 LEU  32     36.555 67.267  3.181 1.00 30.97      A1
ATOM  217 C  LEU  32      34.133 63.597  4.518 1.00 27.87      A1
ATOM  218 O  LEU  32      33.169 63.889  5.250 1.00 25.93      A1
ATOM  219 N  GLN  33      -33.977 63.028  3.315 1.00 27.51      A1
ATOM  220 H  GLN  33      34.787 62.826  2.802 1.00  0.00      A1
ATOM  221 CA GLN  33      32.687 62.671  2.775 1.00 30.40      A1
ATOM  222 CB GLN  33      32.737 61.721  1.614 1.00 29.47      A1
ATOM  223 CG GLN  33      32.888 62.584  0.436 1.00 29.26      A1
ATOM  224 CD GLN  33      33.015 61.869 -0.887 1.00 30.21      A1
ATOM  225 OE1 GLN  33     34.064 61.495 -1.452 1.00 29.61      A1
ATOM  226 NE2 GLN  33     31.823 61.759 -1.426 1.00 33.19      A1
ATOM  227 HE21 GLN  33    31.781 61.128 -2.202 1.00  0.00      A1
ATOM  228 HE22 GLN  33    31.042 62.060 -0.914 1.00  0.00      A1
ATOM  229 C  GLN  33      31.819 61.963  3.788 1.00 35.60      A1
ATOM  230 O  GLN  33      30.715 62.416  4.073 1.00 36.49      A1
ATOM  231 N  GLU  34      32.386 60.925  4.418 1.00 39.81      A1
ATOM  232 H  GLU  34      33.340 60.707  4.328 1.00  0.00      A1
ATOM  233 CA GLU  34      31.541 60.131  5.304 1.00 43.24      A1
ATOM  234 CB GLU  34      32.228 58.792  5.571 1.00 46.46      A1
ATOM  235 CG GLU  34      33.274 58.721  6.624 1.00 55.01      A1
ATOM  236 CD GLU  34      32.777 58.092  7.930 1.00 60.29      A1
ATOM  237 OE1 GLU  34     33.483 57.186  8.412 1.00 63.26      A1
ATOM  238 OE2 GLU  34     31.724 58.504  8.459 1.00 60.44      A1
ATOM  239 C  GLU  34      31.218 60.877  6.564 1.00 43.59      A1
ATOM  240 O  GLU  34      30.175 60.631  7.161 1.00 44.87      A1
ATOM  241 N  LYS  35      32.045 61.811  6.998 1.00 44.80      A1
ATOM  242 H  LYS  35      32.923 61.931  6.569 1.00  0.00      A1
ATOM  243 CA LYS  35      31.674 62.634  8.134 1.00 45.43      A1
ATOM  244 CB LYS  35      32.881 63.364  8.686 1.00 47.67      A1
ATOM  245 CG LYS  35      33.701 62.414  9.510 1.00 52.75      A1
ATOM  246 CD LYS  35      35.084 63.021  9.548 1.00 57.55      A1
ATOM  247 CE LYS  35      36.067 62.099 10.238 1.00 60.35      A1
ATOM  248 NZ LYS  35      35.810 62.064 11.669 1.00 62.91      A1
ATOM  249 HZ1 LYS  35     34.838 61.733 11.840 1.00  0.00      A1
ATOM  250 HZ2 LYS  35     35.930 63.011 12.078 1.00  0.00      A1
ATOM  251 HZ3 LYS  35     36.477 61.405 12.119 1.00  0.00      A1
ATOM  252 C  LYS  35      30.630 63.660  7.697 1.00 44.45      A1
ATOM  253 O  LYS  35      29.730 63.999  8.478 1.00 44.61      A1
ATOM  254 N  LEU  36      30.652 64.190  6.480 1.00 41.21      A1
ATOM  255 H  LEU  36      31.343 63.930  5.836 1.00  0.00      A1
ATOM  256 CA LEU  36      29.647 65.157  6.144 1.00 40.25      A1
ATOM  257 CB LEU  36      30.070 65.899  4.889 1.00 39.01      A1
ATOM  258 CG LEU  36      31.253 66.834  4.935 1.00 43.99      A1
ATOM  259 CD1 LEU  36     31.438 67.404  3.571 1.00 42.08      A1
ATOM  260 CD2 LEU  36     31.034 67.939  5.928 1.00 45.05      A1
ATOM  261 C  LEU  36      28.332 64.414  5.941 1.00 41.90      A1
ATOM  262 O  LEU  36      27.267 64.828  6.431 1.00 42.30      A1
ATOM  263 N  CYS  37      28.392 63.251  5.309 1.00 42.64      A1
ATOM  264 H  CYS  37      29.250 62.904  5.020 1.00  0.00      A1
ATOM  265 CA CYS  37      27.216 62.469  5.084 1.00 43.54      A1
ATOM  266 C  CYS  37      26.638 62.026  6.362 1.00 44.65      A1
ATOM  267 O  CYS  37      25.476 61.997  6.459 1.00 46.40      A1
ATOM  268 CB CYS  37      27.474 61.240  4.313 1.00 44.40      A1
ATOM  269 SG CYS  37      26.133 60.038  4.530 1.00 43.86      A1
ATOM  270 N  ALA  38      27.465 61.734  7.342 1.00 45.96      A1
ATOM  271 H  ALA  38      28.433 61.707  7.202 1.00  0.00      A1
ATOM  272 CA ALA  38      26.932 61.261  8.592 1.00 48.03      A1
ATOM  273 CB ALA  38      27.869 60.440  9.108 1.00 48.64      A1
ATOM  274 C  ALA  38      26.748 62.358  9.624 1.00 48.89      A1
ATOM  275 O  ALA  38      26.103 62.085 10.621 1.00 50.72      A1
ATOM  276 N  THR  39      27.256 63.590  9.512 1.00 50.66      A1
ATOM  277 H  THR  39      27.858 63.780  8.770 1.00  0.00      A1
ATOM  278 CA THR  39      26.976 64.638 10.503 1.00 51.54      A1
ATOM  279 CB THR  39      28.179 65.593 10.690 1.00 51.76      A1
ATOM  280 OG1 THR  39     29.294 64.876 11.176 1.00 51.65      A1
ATOM  281 HG1 THR  39     29.749 64.481 10.355 1.00  0.00      A1
ATOM  282 CG2 THR  39     27.900 66.655 11.729 1.00 51.62      A1
ATOM  283 C  THR  39      25.775 65.466 10.037 1.00 52.17      A1
ATOM  284 O  THR  39      24.886 65.882 10.781 1.00 52.15      A1
ATOM  285 N  TYR  40      25.751 65.720  8.738 1.00 52.83      A1
ATOM  286 H  TYR  40      26.420 65.331  8.139 1.00  0.00      A1
ATOM  287 CA TYR  40      24.729 66.561  8.165 1.00 52.54      A1
ATOM  288 CB TYR  40      25.314 67.872  7.696 1.00 52.15      A1
ATOM  289 CG TYR  40      26.399 68.458  8.552 1.00 54.11      A1
ATOM  290 CD1 TYR  40     27.678 68.341  8.062 1.00 56.50      A1
ATOM  291 CE1 TYR  40     28.719 68.934  8.724 1.00 58.28      A1
ATOM  292 CD2 TYR  40     26.122 69.144  9.716 1.00 54.86      A1
ATOM  293 CE2 TYR  40     27.170 69.736 10.378 1.00 56.20      A1
ATOM  294 CZ TYR  40      28.453 69.642  9.872 1.00 58.26      A1
ATOM  295 OH TYR  40      29.513 70.310 10.463 1.00 61.00      A1
ATOM  296 HH TYR  40      30.179 70.443  9.782 1.00  0.00      A1
ATOM  297 C  TYR  40      24.035 65.911  6.981 1.00 51.75      A1
ATOM  298 O  TYR  40      23.662 66.578  6.024 1.00 52.52      A1
ATOM  299 N  LYS  41      23.941 64.600  6.965 1.00 50.54      A1
ATOM  300 H  LYS  41      24.474 64.064  7.583 1.00  0.00      A1
ATOM  301 CA LYS  41      23.112 63.885  6.029 1.00 50.48      A1
ATOM  302 CB LYS  41      21.641 63.989  6.540 1.00 50.62      A1
ATOM  303 CG LYS  41      21.387 63.326  7.911 1.00 52.81      A1
ATOM  304 CD LYS  41      20.112 63.878  8.574 1.00 55.54      A1
```

FIGURE 5

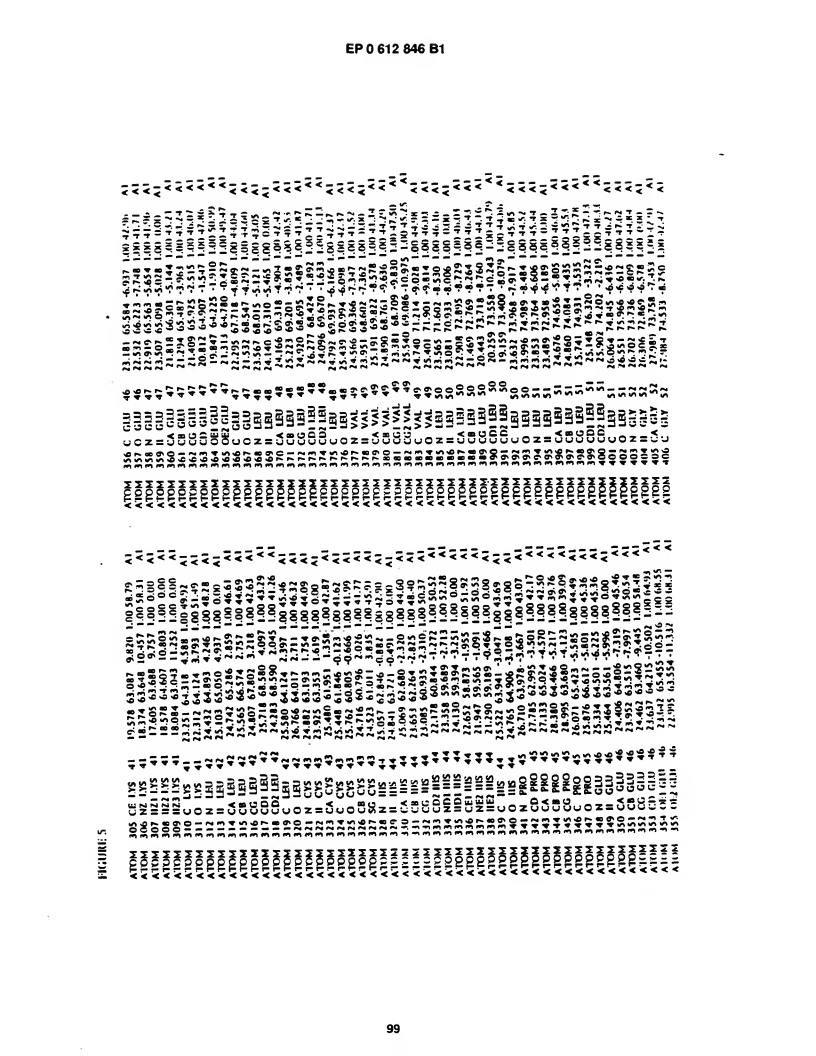


FIGURE 5

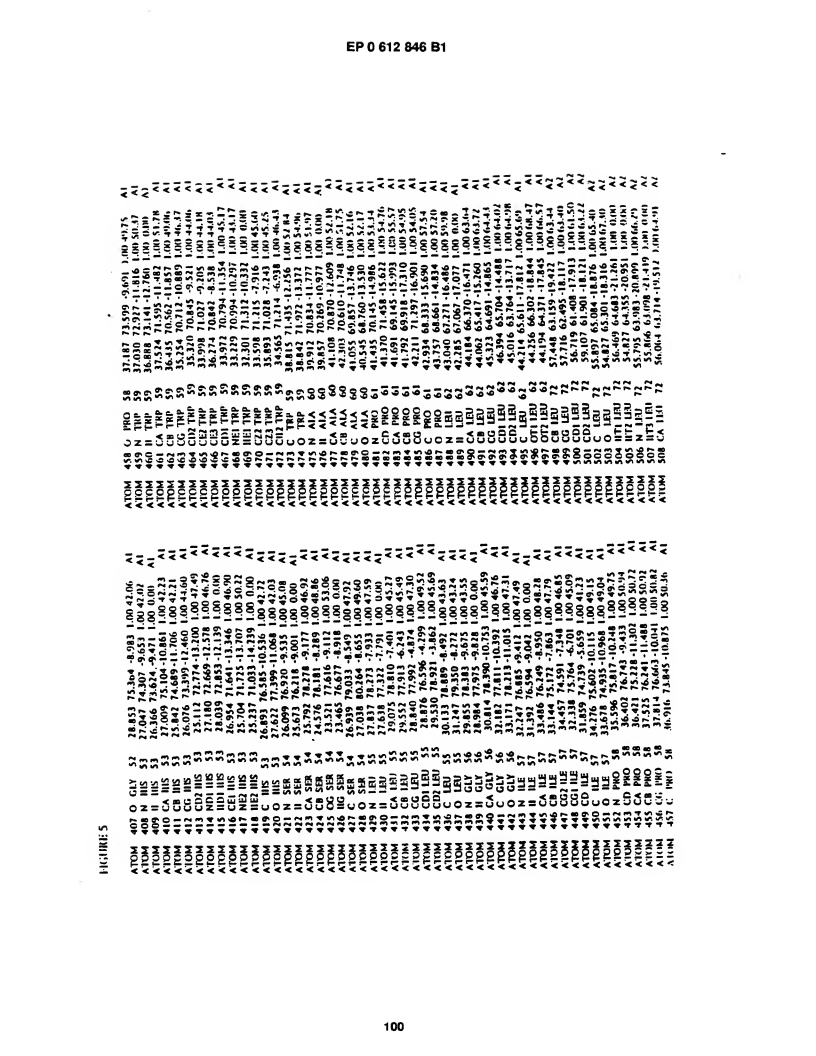


FIGURE 5

FIGURE 5

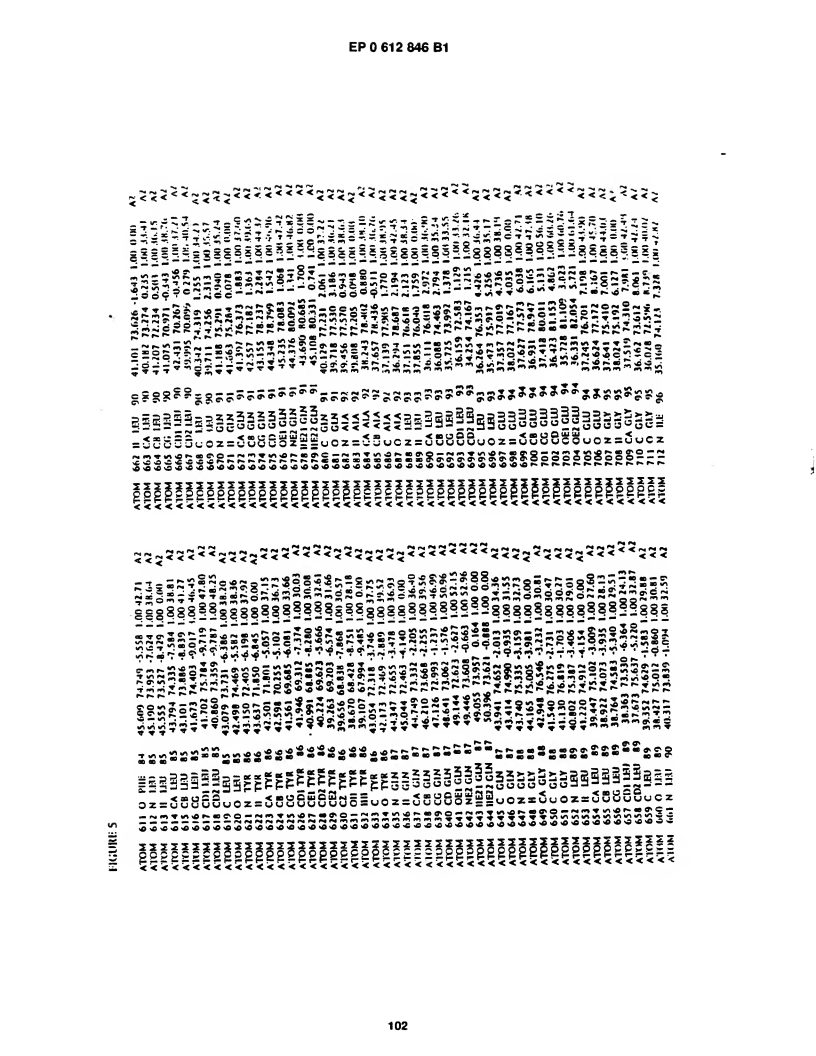


FIGURE 5

```
ATOM  713 H  ILE  96      35.357 74.944  6.841  1.00  0.00      A2
ATOM  714 CA ILE  96      33.760 73.692  7.312  1.00 42.12      A2
ATOM  715 CB ILE  96      33.665 72.233  6.800  1.00 36.31      A2
ATOM  716 CG2 ILE  96      32.248 71.768  6.789  1.00 34.79      A2
ATOM  717 CG1 ILE  96      34.091 72.157  5.374  1.00 35.35      A2
ATOM  718 CD ILE  96      34.051 70.743  4.738  1.00 33.64      A2
ATOM  719 C  ILE  96      33.106 73.863  8.709  1.00 44.74      A2
ATOM  720 O  ILE  96      32.220 74.716  8.841  1.00 44.59      A2
ATOM  721 N  SER  97      33.467 73.154  9.780  1.00 46.84      A2
ATOM  722 H  SER  97      34.243 72.553  9.706  1.00  0.00      A2
ATOM  723 CA SER  97      32.900 73.359 11.105  1.00 48.91      A2
ATOM  724 CB SER  97      31.804 72.343 11.347  1.00 49.60      A2
ATOM  725 OG SER  97      32.211 71.120 11.954  1.00 52.85      A2
ATOM  726 HG SER  97      31.406 70.573 11.942  1.00  0.00      A2
ATOM  727 C  SER  97      34.045 73.143 12.077  1.00 50.64      A2
ATOM  728 O  SER  97      35.035 72.538 11.678  1.00 52.78      A2
ATOM  729 N  PRO  98      34.063 73.474 13.348  1.00 52.12      A2
ATOM  730 CD PRO  98      33.002 74.170 14.016  1.00 52.90      A2
ATOM  731 CA PRO  98      35.195 73.200 14.257  1.00 54.94      A2
ATOM  732 CB PRO  98      34.750 73.717 15.600  1.00 54.78      A2
ATOM  733 CG PRO  98      33.772 74.777 15.182  1.00 55.48      A2
ATOM  734 C  PRO  98      35.591 71.723 14.336  1.00 56.75      A2
ATOM  735 O  PRO  98      36.738 71.274 14.468  1.00 57.85      A2
ATOM  736 N  GLU  99      34.509 70.971 14.414  1.00 58.21      A2
ATOM  737 H  GLU  99      33.652 71.400 14.028  1.00  0.00      A2
ATOM  738 CA GLU  99      34.543 69.537 14.481  1.00 58.48      A2
ATOM  739 CB GLU  99      33.111 69.104 14.304  1.00 63.30      A2
ATOM  740 CG GLU  99      32.958 67.702 14.852  1.00 71.04      A2
ATOM  741 CD GLU  99      32.076 66.838 13.968  1.00 76.95      A2
ATOM  742 OE1 GLU  99      32.209 65.608 14.079  1.00 80.63      A2
ATOM  743 OE2 GLU  99      31.295 67.382 13.153  1.00 77.99      A2
ATOM  744 C  GLU  99      35.298 69.025 13.074  1.00 55.31      A2
ATOM  745 O  GLU  99      36.251 68.270 13.210  1.00 55.96      A2
ATOM  746 N  LEU 100      34.916 69.475 11.891  1.00 51.23      A2
ATOM  747 H  LEU 100      34.214 70.159 11.841  1.00  0.00      A2
ATOM  748 CA LEU 100      35.577 69.052 10.678  1.00 48.08      A2
ATOM  749 CB LEU 100      34.627 69.341  9.574  1.00 45.52      A2
ATOM  750 CG LEU 100      33.544 68.337  9.674  1.00 45.39      A2
ATOM  751 CD1 LEU 100      32.207 68.972  9.458  1.00 46.40      A2
ATOM  752 CD2 LEU 100      33.851 67.245  8.677  1.00 47.48      A2
ATOM  753 C  LEU 100      36.958 69.638 10.368  1.00 46.77      A2
ATOM  754 O  LEU 100      37.578 69.244  9.357  1.00 46.62      A2
ATOM  755 N  GLY 101      37.441 70.505 11.272  1.00 45.40      A2
ATOM  756 H  GLY 101      36.893 70.704 12.056  1.00  0.00      A2
ATOM  757 CA GLY 101      38.703 71.238 11.126  1.00 42.52      A2
ATOM  758 C  GLY 101      39.885 70.334 10.798  1.00 40.73      A2
ATOM  759 O  GLY 101      40.475 70.402  9.710  1.00 40.69      A2
ATOM  760 N  PRO 102      40.250 69.441 11.708  1.00 38.61      A2
ATOM  761 CD PRO 102      39.676 69.350 13.027  1.00 39.26      A2
ATOM  762 CA PRO 102      41.390 68.566 11.606  1.00 37.30      A2
ATOM  763 CB PRO 102      41.294 67.690 12.775  1.00 39.36      A2
ATOM  764 CG PRO 102      40.799 68.687 13.776  1.00 41.02      A2
ATOM  765 C  PRO 102      41.364 67.795 10.331  1.00 37.15      A2
ATOM  766 O  PRO 102      42.358 67.854  9.605  1.00 38.88      A2
ATOM  767 N  THR 103      40.223 67.167 10.045  1.00 35.36      A2
ATOM  768 H  THR 103      39.466 67.223 10.662  1.00  0.00      A2
ATOM  769 CA THR 103      40.051 66.386  8.843  1.00 34.62      A2
ATOM  770 CB THR 103      38.592 65.888  8.715  1.00 34.07      A2
ATOM  771 OG1 THR 103      38.356 65.240  9.936  1.00 35.43      A2
ATOM  772 HG1 THR 103      38.011 65.896 10.548  1.00  0.00      A2
ATOM  773 CG2 THR 103      38.312 64.896  7.594  1.00 31.29      A2
ATOM  774 C  THR 103      40.417 67.215  7.625  1.00 31.79      A2
ATOM  775 O  THR 103      41.091 66.665  6.738  1.00 30.16      A2
ATOM  776 N  LEU 104      40.054 68.498  7.529  1.00 32.49      A2
ATOM  777 H  LEU 104      39.504 68.923  8.229  1.00  0.00      A2
ATOM  778 CA LEU 104      40.471 69.267  6.370  1.00 30.49      A2
ATOM  779 CB LEU 104      39.616 70.430  6.242  1.00 33.51      A2
ATOM  780 CG LEU 104      38.356 69.996  5.611  1.00 36.61      A2
ATOM  781 CD1 LEU 104      37.222 70.621  6.381  1.00 39.43      A2
ATOM  782 CD2 LEU 104      38.448 70.294  4.132  1.00 37.89      A2
ATOM  783 C  LEU 104      41.904 69.727  6.414  1.00 28.48      A2
ATOM  784 O  LEU 104      42.583 69.825  5.398  1.00 28.47      A2
ATOM  785 N  ASP 105      42.449 69.949  7.574  1.00 26.99      A2
ATOM  786 H  ASP 105      41.903 69.912  8.388  1.00  0.00      A2
ATOM  787 CA ASP 105      43.822 70.307  7.613  1.00 28.67      A2
ATOM  788 CB ASP 105      44.139 70.584  9.038  1.00 33.06      A2
ATOM  789 CG ASP 105      43.438 71.808  9.593  1.00 35.46      A2
ATOM  790 OD1 ASP 105      43.085 72.726  8.836  1.00 38.53      A2
ATOM  791 OD2 ASP 105      43.244 71.816 10.808  1.00 39.10      A2
ATOM  792 C  ASP 105      44.701 69.206  7.032  1.00 28.90      A2
ATOM  793 O  ASP 105      45.551 69.479  6.175  1.00 29.62      A2
ATOM  794 N  THR 106      44.415 67.950  7.401  1.00 26.86      A2
ATOM  795 H  THR 106      43.674 67.826  8.029  1.00  0.00      A2
ATOM  796 CA THR 106      45.143 66.770  6.935  1.00 24.81      A2
ATOM  797 CB THR 106      44.558 65.456  7.477  1.00 26.03      A2
ATOM  798 OG1 THR 106      44.680 65.566  8.894  1.00 31.53      A2
ATOM  799 HG1 THR 106      44.069 66.223  9.242  1.00  0.00      A2
ATOM  800 CG2 THR 106      45.258 64.220  7.011  1.00 20.90      A2
ATOM  801 C  THR 106      45.073 66.684  5.460  1.00 23.75      A2
ATOM  802 O  THR 106      46.065 66.411  4.812  1.00 24.58      A2
ATOM  803 N  LEU 107      43.887 66.917  4.946  1.00 24.30      A2
ATOM  804 H  LEU 107      43.145 67.176  5.528  1.00  0.00      A2
ATOM  805 CA LEU 107      43.668 66.783  3.531  1.00 27.29      A2
ATOM  806 CB LEU 107      42.158 66.913  3.273  1.00 25.45      A2
ATOM  807 CG LEU 107      41.642 66.888  1.863  1.00 26.24      A2
ATOM  808 CD1 LEU 107      42.095 65.649  1.158  1.00 26.41      A2
ATOM  809 CD2 LEU 107      40.140 66.925  1.914  1.00 27.62      A2
ATOM  810 C  LEU 107      44.485 67.848  2.819  1.00 28.03      A2
ATOM  811 O  LEU 107      45.154 67.555  1.823  1.00 30.72      A2
ATOM  812 N  GLN 108      44.540 69.055  3.373  1.00 28.52      A2
ATOM  813 H  GLN 108      44.030 69.221  4.194  1.00  0.00      A2
ATOM  814 CA GLN 108      45.343 70.132  2.792  1.00 28.48      A2
```

FIGURE 5

```
ATOM  815 CB  GLN  108      45.138  71.363   3.630  1.00 30.15      A2
ATOM  816 CG  GLN  108      43.711  71.787   3.542  1.00 32.67      A2
ATOM  817 CD  GLN  108      43.606  73.192   4.048  1.00 35.24      A2
ATOM  818 OE1 GLN  108      43.085  73.484   5.125  1.00 36.07      A2
ATOM  819 NE2 GLN  108      44.189  74.044   3.213  1.00 33.58      A2
ATOM  820 HE21 GLN  108     44.582  73.701   2.386  1.00  0.00      A2
ATOM  821 HE22 GLN  108     44.195  74.986   3.471  1.00  0.00      A2
ATOM  822 C   GLN  108      46.840  69.842   2.675  1.00 26.40      A2
ATOM  823 O   GLN  108      47.450  69.955   1.597  1.00 27.57      A2
ATOM  824 N   LEU  109      47.388  69.473   3.833  1.00 25.81      A2
ATOM  825 H   LEU  109      46.795  69.495   4.615  1.00  0.00      A2
ATOM  826 CA  LEU  109      48.764  69.003   4.043  1.00 27.96      A2
ATOM  827 CB  LEU  109      48.951  68.637   5.513  1.00 29.41      A2
ATOM  828 CG  LEU  109      48.712  69.771   6.520  1.00 31.78      A2
ATOM  829 CD1 LEU  109      48.750  69.188   7.933  1.00 29.16      A2
ATOM  830 CD2 LEU  109      49.724  70.889   6.285  1.00 32.19      A2
ATOM  831 C   LEU  109      -49.168  67.790   3.186  1.00 26.80      A2
ATOM  832 O   LEU  109      50.214  67.721   2.544  1.00 26.81      A2
ATOM  833 N   ASP  110      48.305  66.807   3.090  1.00 25.98      A2
ATOM  834 H   ASP  110      47.471  66.835   3.600  1.00  0.00      A2
ATOM  835 CA  ASP  110      48.590  65.684   2.250  1.00 23.32      A2
ATOM  836 CB  ASP  110      47.577  64.570   2.553  1.00 26.34      A2
ATOM  837 CG  ASP  110      47.905  63.878   3.894  1.00 31.10      A2
ATOM  838 OD1 ASP  110      47.070  63.093   4.323  1.00 34.98      A2
ATOM  839 OD2 ASP  110      -48.958  64.107   4.535  1.00 34.06      A2
ATOM  840 C   ASP  110      48.557  66.338   0.842  1.00 21.31      A2
ATOM  841 O   ASP  110      49.493  65.711   0.165  1.00 20.63      A2
ATOM  842 N   VAL  111      47.627  66.998   0.363  1.00 20.80      A2
ATOM  843 H   VAL  111      46.900  67.310   0.944  1.00  0.00      A2
ATOM  844 CA  VAL  111      47.711  67.454   -1.019  1.00 20.44      A2
ATOM  845 CB  VAL  111      46.531  68.364   -1.376  1.00 23.60      A2
ATOM  846 CG1 VAL  111      46.615  68.946   -2.808  1.00 23.04      A2
ATOM  847 CG2 VAL  111      45.289  67.497   -1.371  1.00 24.30      A2
ATOM  848 C   VAL  111      49.006  68.253   -1.245  1.00 19.22      A2
ATOM  849 O   VAL  111      49.617  68.006   -2.303  1.00 19.22      A2
ATOM  850 N   ALA  112      49.442  69.063   -0.267  1.00 21.84      A2
ATOM  851 H   ALA  112      48.839  69.190   0.492  1.00  0.00      A2
ATOM  852 CA  ALA  112      50.708  69.805   -0.295  1.00 24.16      A2
ATOM  853 CB  ALA  112      50.861  70.561   1.011  1.00 22.69      A2
ATOM  854 C   ALA  112      51.931  68.878   -0.486  1.00 28.58      A2
ATOM  855 O   ALA  112      52.778  69.026   -1.390  1.00 32.53      A2
ATOM  856 N   ASP  113      52.086  67.852   0.343  1.00 30.21      A2
ATOM  857 H   ASP  113      51.507  67.817   1.130  1.00  0.00      A2
ATOM  858 CA  ASP  113      53.084  66.846   0.166  1.00 31.70      A2
ATOM  859 CB  ASP  113      52.706  65.659   0.953  1.00 36.31      A2
ATOM  860 CG  ASP  113      53.170  65.758   2.357  1.00 42.27      A2
ATOM  861 OD1 ASP  113      52.559  65.109   3.203  1.00 46.37      A2
ATOM  862 OD2 ASP  113      54.160  66.461   2.589  1.00 48.93      A2
ATOM  863 C   ASP  113      53.315  66.361   -1.239  1.00 32.82      A2
ATOM  864 O   ASP  113      54.413  66.308   -1.754  1.00 36.25      A2
ATOM  865 N   PHE  114      52.187  65.978   -1.830  1.00 30.94      A2
ATOM  866 H   PHE  114      51.344  66.164   -1.361  1.00  0.00      A2
ATOM  867 CA  PHE  114      52.109  65.328   -3.103  1.00 27.84      A2
ATOM  868 CB  PHE  114      50.708  64.794   -3.226  1.00 25.18      A2
ATOM  869 CG  PHE  114      50.565  63.928   -4.420  1.00 21.04      A2
ATOM  870 CD1 PHE  114      51.623  63.225   -4.938  1.00 18.05      A2
ATOM  871 CD2 PHE  114      49.369  63.814   -5.046  1.00 22.37      A2
ATOM  872 CE1 PHE  114      51.476  62.514   -6.102  1.00 24.54      A2
ATOM  873 CE2 PHE  114      49.211  63.207   -6.212  1.00 21.33      A2
ATOM  874 CZ  PHE  114      50.263  62.509   -6.741  1.00 24.71      A2
ATOM  875 C   PHE  114      52.453  66.291   -4.190  1.00 29.20      A2
ATOM  876 O   PHE  114      53.072  65.883   -5.158  1.00 30.84      A2
ATOM  877 N   ALA  115      52.057  67.554   -4.058  1.00 31.99      A2
ATOM  878 H   ALA  115      51.446  67.768   -3.317  1.00  0.00      A2
ATOM  879 CA  ALA  115      52.423  68.655   -4.952  1.00 31.29      A2
ATOM  880 CB  ALA  115      51.824  69.939   -4.420  1.00 30.65      A2
ATOM  881 C   ALA  115      53.936  68.787   -4.976  1.00 31.31      A2
ATOM  882 O   ALA  115      54.539  68.823   -6.044  1.00 30.86      A2
ATOM  883 N   THR  116      54.551  68.846   -3.813  1.00 32.20      A2
ATOM  884 H   THR  116      54.013  68.910   -2.992  1.00  0.00      A2
ATOM  885 CA  THR  116      55.998  68.897   -3.656  1.00 34.91      A2
ATOM  886 CB  THR  116      56.325  68.953   -2.150  1.00 35.78      A2
ATOM  887 OG1 THR  116      55.364  70.038   -1.576  1.00 39.58      A2
ATOM  888 HG1 THR  116      54.942  69.644   -0.939  1.00  0.00      A2
ATOM  889 CG2 THR  116      57.816  69.050   -1.921  1.00 35.08      A2
ATOM  890 C   THR  116      56.714  67.726   -4.304  1.00 37.14      A2
ATOM  891 O   THR  116      57.641  67.937   -5.066  1.00 39.42      A2
ATOM  892 N   THR  117      56.318  66.485   -4.045  1.00 39.05      A2
ATOM  893 H   THR  117      55.615  66.383   -3.369  1.00  0.00      A2
ATOM  894 CA  THR  117      56.840  65.269   -4.630  1.00 40.23      A2
ATOM  895 CB  THR  117      55.909  64.090   -4.216  1.00 39.99      A2
ATOM  896 OG1 THR  117      56.149  63.920   -2.820  1.00 40.66      A2
ATOM  897 HG1 THR  117      55.653  64.559   -2.286  1.00  0.00      A2
ATOM  898 CG2 THR  117      56.110  62.781   -4.981  1.00 38.23      A2
ATOM  899 C   THR  117      56.882  65.417   -6.134  1.00 44.52      A2
ATOM  900 O   THR  117      57.934  65.253   -6.749  1.00 46.29      A2
ATOM  901 N   ILE  118      55.763  65.777   -6.741  1.00 45.87      A2
ATOM  902 H   ILE  118      54.962  65.942   -6.200  1.00  0.00      A2
ATOM  903 CA  ILE  118      55.659  65.914   -8.182  1.00 47.97      A2
ATOM  904 C8  ILE  118      54.170  66.271   -8.452  1.00 47.69      A2
ATOM  905 CG2 ILE  118      54.041  66.930   -9.835  1.00 47.03      A2
ATOM  906 CG1 ILE  118      53.302  65.011   -8.244  1.00 44.00      A2
ATOM  907 CD  ILE  118      53.651  63.883   -9.236  1.00 44.52      A2
ATOM  908 C   ILE  118      56.647  66.932   -8.724  1.00 50.69      A2
ATOM  909 O   ILE  118      57.390  66.676   -9.681  1.00 49.98      A2
ATOM  910 N   TRP  119      56.697  68.061   -8.015  1.00 54.68      A2
ATOM  911 H   TRP  119      56.164  68.135   -7.197  1.00  0.00      A2
ATOM  912 CA  TRP  119      57.575  69.142   -8.399  1.00 58.98      A2
ATOM  913 CB  TRP  119      57.392  70.367   -7.477  1.00 59.84      A2
ATOM  914 CG  TRP  119      58.051  71.529   -8.196  1.00 62.64      A2
ATOM  915 CD2 TRP  119      57.596  72.211   -9.307  1.00 64.78      A2
ATOM  916 CE2 TRP  119      58.699  72.955   -9.643  1.00 62.55      A2
```

FIGURE 5

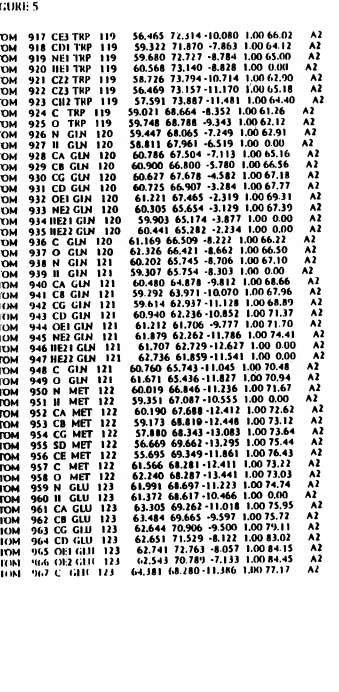

ATOM 917 CE3 TRP 119 56.465 72.514 -10.080 1.00 66.02 A2
ATOM 918 CD1 TRP 119 59.322 71.870 -7.863 1.00 64.12 A2
ATOM 919 NE1 TRP 119 59.680 72.727 -8.784 1.00 65.00 A2
ATOM 920 HE1 TRP 119 60.568 73.140 -8.828 1.00 0.00 A2
ATOM 921 CZ2 TRP 119 58.726 73.794 -10.714 1.00 62.90 A2
ATOM 922 CZ3 TRP 119 56.469 73.157 -11.170 1.00 65.18 A2
ATOM 923 CH2 TRP 119 57.591 73.887 -11.481 1.00 64.40 A2
ATOM 924 C TRP 119 59.021 68.664 -8.352 1.00 61.26 A2
ATOM 925 O TRP 119 59.748 68.788 -9.343 1.00 62.12 A2
ATOM 926 N GLN 120 59.447 68.065 -7.249 1.00 67.91 A2
ATOM 927 H GLN 120 58.811 67.961 -6.519 1.00 0.00 A2
ATOM 928 CA GLN 120 60.786 67.504 -7.113 1.00 65.16 A2
ATOM 929 CB GLN 120 60.900 66.800 -5.780 1.00 66.56 A2
ATOM 930 CG GLN 120 60.627 67.678 -4.582 1.00 67.18 A2
ATOM 931 CD GLN 120 60.725 66.907 -3.284 1.00 67.77 A2
ATOM 932 OE1 GLN 120 61.221 67.465 -2.319 1.00 69.31 A2
ATOM 933 NE2 GLN 120 60.305 65.654 -3.129 1.00 67.39 A2
ATOM 934 HE21 GLN 120 59.903 65.174 -3.877 1.00 0.00 A2
ATOM 935 HE22 GLN 120 60.441 65.282 -2.234 1.00 0.00 A2
ATOM 936 C GLN 120 61.169 66.509 -8.222 1.00 66.22 A2
ATOM 937 O GLN 120 62.326 66.421 -8.662 1.00 66.50 A2
ATOM 938 N GLN 121 60.202 65.745 -8.706 1.00 67.10 A2
ATOM 939 H GLN 121 59.307 65.754 -8.303 1.00 0.00 A2
ATOM 940 CA GLN 121 60.480 64.878 -9.812 1.00 68.66 A2
ATOM 941 CB GLN 121 59.292 63.971 -10.070 1.00 67.96 A2
ATOM 942 CG GLN 121 59.614 62.937 -11.128 1.00 68.89 A2
ATOM 943 CD GLN 121 60.940 62.236 -10.852 1.00 71.37 A2
ATOM 944 OE1 GLN 121 61.212 61.706 -9.777 1.00 71.70 A2
ATOM 945 NE2 GLN 121 61.879 62.262 -11.786 1.00 74.41 A2
ATOM 946 HE21 GLN 121 61.707 62.729 -12.627 1.00 0.00 A2
ATOM 947 HE22 GLN 121 62.736 61.859 -11.541 1.00 0.00 A2
ATOM 948 C GLN 121 60.760 65.743 -11.045 1.00 70.48 A2
ATOM 949 O GLN 121 61.671 65.436 -11.827 1.00 70.94 A2
ATOM 950 N MET 122 60.019 66.846 -11.236 1.00 71.67 A2
ATOM 951 H MET 122 59.351 67.087 -10.555 1.00 0.00 A2
ATOM 952 CA MET 122 60.190 67.688 -12.412 1.00 72.62 A2
ATOM 953 CB MET 122 59.173 68.819 -12.448 1.00 73.12 A2
ATOM 954 CG MET 122 57.880 68.343 -13.083 1.00 73.64 A2
ATOM 955 SD MET 122 56.669 69.662 -13.295 1.00 75.44 A2
ATOM 956 CE MET 122 55.695 69.349 -11.861 1.00 76.43 A2
ATOM 957 C MET 122 61.566 68.281 -12.411 1.00 73.22 A2
ATOM 958 O MET 122 62.240 68.287 -13.441 1.00 73.03 A2
ATOM 959 N GLU 123 61.991 68.697 -11.223 1.00 74.74 A2
ATOM 960 H GLU 123 61.377 68.617 -10.466 1.00 0.00 A2
ATOM 961 CA GLU 123 63.305 69.262 -11.018 1.00 75.95 A2
ATOM 962 CB GLU 123 63.484 69.665 -9.597 1.00 75.72 A2
ATOM 963 CG GLU 123 62.644 70.906 -9.500 1.00 79.11 A2
ATOM 964 CD GLU 123 62.651 71.529 -8.122 1.00 83.02 A2
ATOM 965 OE1 GLU 123 62.741 72.763 -8.057 1.00 84.15 A2
ATOM 966 OE2 GLU 123 62.543 70.789 -7.133 1.00 84.45 A2
ATOM 967 C GLU 123 64.381 68.280 -11.386 1.00 77.17 A2
ATOM 968 O GLU 123 65.092 68.558 -12.356 1.00 78.22 A2
ATOM 969 N GLU 124 64.504 67.130 -10.765 1.00 77.86 A2
ATOM 970 H GLU 124 63.867 66.852 -10.060 1.00 0.00 A2
ATOM 971 CA GLU 124 65.574 66.215 -11.167 1.00 78.47 A2
ATOM 972 CB GLU 124 65.600 65.051 -10.195 1.00 80.29 A2
ATOM 973 CG GLU 124 64.387 64.132 -10.150 1.00 83.29 A2
ATOM 974 CD GLU 124 64.375 63.248 -8.908 1.00 85.53 A2
ATOM 975 OE1 GLU 124 64.733 63.729 -7.824 1.00 86.84 A2
ATOM 976 OE2 GLU 124 64.006 62.075 -9.024 1.00 86.39 A2
ATOM 977 C GLU 124 65.534 65.705 -12.612 1.00 78.01 A2
ATOM 978 O GLU 124 66.480 65.057 -13.060 1.00 78.91 A2
ATOM 979 N LEU 125 64.460 65.943 -13.363 1.00 77.11 A2
ATOM 980 H LEU 125 63.666 66.340 -12.945 1.00 0.00 A2
ATOM 981 CA LEU 125 64.387 65.583 -14.771 1.00 76.23 A2
ATOM 982 CB LEU 125 63.061 64.832 -14.952 1.00 76.88 A2
ATOM 983 CG LEU 125 62.392 64.382 -16.263 1.00 76.63 A2
ATOM 984 CD1 LEU 125 63.350 63.754 -17.276 1.00 76.67 A2
ATOM 985 CD2 LEU 125 61.309 63.402 -15.839 1.00 75.89 A2
ATOM 986 C LEU 125 64.506 66.827 -15.648 1.00 75.84 A2
ATOM 987 O LEU 125 64.360 66.788 -16.871 1.00 75.56 A2
ATOM 988 N GLY 126 64.759 67.968 -15.027 1.00 75.90 A2
ATOM 989 H GLY 126 64.741 67.976 -14.056 1.00 0.00 A2
ATOM 990 CA GLY 126 64.968 69.213 -15.736 1.00 77.58 A2
ATOM 991 C GLY 126 63.697 69.814 -16.330 1.00 78.63 A2
ATOM 992 O GLY 126 63.735 70.736 -17.146 1.00 78.55 A2
ATOM 993 N MET 127 62.524 69.343 -15.933 1.00 80.08 A2
ATOM 994 H MET 127 62.522 68.503 -15.393 1.00 0.00 A2
ATOM 995 CA MET 127 61.266 69.902 -16.415 1.00 81.46 A2
ATOM 996 CB MET 127 60.191 68.802 -16.361 1.00 81.86 A2
ATOM 997 CG MET 127 60.708 67.599 -17.147 1.00 82.66 A2
ATOM 998 SD MET 127 59.682 66.115 -17.218 1.00 83.70 A2
ATOM 999 CE MET 127 60.236 65.620 -18.900 1.00 84.23 A2
ATOM 1000 C MET 127 60.847 71.131 -15.599 1.00 82.18 A2
ATOM 1001 OT1 MET 127 60.116 71.958 -16.142 1.00 83.86 A2
ATOM 1002 OT2 MET 127 61.267 71.285 -14.446 1.00 82.84 A2
ATOM 1003 CB MET 138 39.323 80.595 -4.492 1.00 59.29 A3
ATOM 1004 CG MET 138 40.123 79.298 -4.421 1.00 57.97 A3
ATOM 1005 SD MET 138 40.561 78.973 -6.145 1.00 60.85 A3
ATOM 1006 CE MET 138 41.129 77.310 -6.351 1.00 61.48 A3
ATOM 1007 C MET 138 37.021 81.072 -5.454 1.00 60.26 A3
ATOM 1008 O MET 138 36.832 82.262 -5.181 1.00 62.98 A3
ATOM 1009 1IT1 MET 138 38.497 82.600 -6.075 1.00 0.00 A3
ATOM 1010 1IT2 MET 138 38.313 81.757 -7.529 1.00 0.00 A3
ATOM 1011 N MET 138 38.839 81.784 -6.639 1.00 60.49 A3
ATOM 1012 1IT3 MET 138 39.865 81.816 -6.768 1.00 0.00 A3
ATOM 1013 CA MET 138 38.445 80.672 -7.587 1.00 60.51 A3
ATOM 1014 N PRO 139 35.995 80.242 -5.612 1.00 57.82 A3
ATOM 1015 CD PRO 139 36.028 79.060 -6.448 1.00 58.10 A3
ATOM 1016 CA PRO 139 34.654 80.538 -5.142 1.00 54.67 A3
ATOM 1017 CB PRO 139 33.870 79.323 -5.525 1.00 54.54 A3
ATOM 1018 CG PRO 139 34.945 78.290 -5.755 1.00 58.26 A3

FIGURE 5

```
ATOM  1019 C   PRO  139      34.588  80.675  -3.664  1.00 52.24      A3
ATOM  1020 O   PRO  139      35.507  80.623  -2.882  1.00 51.89      A3
ATOM  1021 N   ALA  140      33.499  81.547  -3.342  1.00 49.86      A3
ATOM  1022 H   ALA  140      32.789  81.676  -4.005  1.00  0.00      A3
ATOM  1023 CA  ALA  140      33.234  81.926  -1.994  1.00 49.39      A3
ATOM  1024 CB  ALA  140      32.966  83.413  -1.895  1.00 49.94      A3
ATOM  1025 C   ALA  140      31.978  81.153  -1.590  1.00 49.25      A3
ATOM  1026 O   ALA  140      30.889  81.162  -2.205  1.00 49.06      A3
ATOM  1027 N   PHE  141      32.293  80.442  -0.506  1.00 47.48      A3
ATOM  1028 H   PHE  141      33.190  80.550  -0.122  1.00  0.00      A3
ATOM  1029 CA  PHE  141      31.401  79.552   0.208  1.00 45.66      A3
ATOM  1030 CB  PHE  141      32.215  78.305   0.792  1.00 40.28      A3
ATOM  1031 CG  PHE  141      32.684  77.404  -0.349  1.00 35.35      A3
ATOM  1032 CD1 PHE  141      31.800  76.591  -1.006  1.00 34.39      A3
ATOM  1033 CD2 PHE  141      33.966  77.497  -0.830  1.00 37.69      A3
ATOM  1034 CE1 PHE  141      32.174  75.895  -2.133  1.00 34.00      A3
ATOM  1035 CE2 PHE  141      34.358  76.807  -1.956  1.00 36.69      A3
ATOM  1036 CZ  PHE  141      33.449  76.001  -2.614  1.00 37.29      A3
ATOM  1037 C   PHE  141      31.003  80.580   1.242  1.00 46.54      A3
ATOM  1038 O   PHE  141      31.584  80.664   2.317  1.00 48.26      A3
ATOM  1039 N   ALA  142      30.067  81.452   0.843  1.00 47.38      A3
ATOM  1040 H   ALA  142      29.624  81.295  -0.020  1.00  0.00      A3
ATOM  1041 CA  ALA  142      29.581  82.564   1.668  1.00 46.06      A3
ATOM  1042 CB  ALA  142      28.731  83.546   0.879  1.00 45.04      A3
ATOM  1043 C   ALA  142      28.703  82.132   2.802  1.00 45.27      A3
ATOM  1044 O   ALA  142      28.343  83.002   3.584  1.00 47.38      A3
ATOM  1045 N   SER  143      28.318  80.860   2.899  1.00 43.36      A3
ATOM  1046 H   SER  143      28.724  80.201   2.303  1.00  0.00      A3
ATOM  1047 CA  SER  143      27.377  80.392   3.897  1.00 41.94      A3
ATOM  1048 CB  SER  143      26.036  80.129   3.181  1.00 44.17      A3
ATOM  1049 OG  SER  143      25.323  78.918   3.536  1.00 48.18      A3
ATOM  1050 HG  SER  143      24.455  78.974   3.098  1.00  0.00      A3
ATOM  1051 C   SER  143      27.877  79.197   4.602  1.00 39.79      A3
ATOM  1052 O   SER  143      28.763  78.452   4.132  1.00 38.50      A3
ATOM  1053 N   ALA  144      27.218  78.775   5.683  1.00 39.10      A3
ATOM  1054 H   ALA  144      26.449  79.312   5.960  1.00  0.00      A3
ATOM  1055 CA  ALA  144      27.566  77.586   6.411  1.00 39.22      A3
ATOM  1056 CB  ALA  144      26.982  77.598   7.802  1.00 36.97      A3
ATOM  1057 C   ALA  144      26.964  76.420   5.627  1.00 41.58      A3
ATOM  1058 O   ALA  144      27.706  75.448   5.444  1.00 42.07      A3
ATOM  1059 N   PHE  145      25.719  76.407   5.076  1.00 40.77      A3
ATOM  1060 H   PHE  145      25.149  77.203   5.110  1.00  0.00      A3
ATOM  1061 CA  PHE  145      25.307  75.234   4.312  1.00 39.31      A3
ATOM  1062 CB  PHE  145      23.877  75.396   3.798  1.00 36.46      A3
ATOM  1063 CG  PHE  145      23.477  74.452   2.641  1.00 31.91      A3
ATOM  1064 CD1 PHE  145      23.579  74.900   1.323  1.00 29.02      A3
ATOM  1065 CD2 PHE  145      23.013  73.185   2.916  1.00 29.40      A3
ATOM  1066 CE1 PHE  145      23.225  74.100   0.277  1.00 28.34      A3
ATOM  1067 CE2 PHE  145      22.661  72.389   1.858  1.00 28.80      A3
ATOM  1068 CZ  PHE  145      22.764  72.831   0.549  1.00 30.58      A3
ATOM  1069 C   PHE  145      26.266  75.071   3.120  1.00 40.44      A3
ATOM  1070 O   PHE  145      26.556  73.938   2.697  1.00 40.55      A3
ATOM  1071 N   GLN  146      26.745  76.232   2.619  1.00 39.11      A3
ATOM  1072 H   GLN  146      26.437  77.073   3.015  1.00  0.00      A3
ATOM  1073 CA  GLN  146      27.660  76.263   1.511  1.00 38.01      A3
ATOM  1074 CB  GLN  146      27.907  77.664   1.054  1.00 38.92      A3
ATOM  1075 CG  GLN  146      26.864  78.066   0.049  1.00 43.26      A3
ATOM  1076 CD  GLN  146      27.171  79.440  -0.522  1.00 45.47      A3
ATOM  1077 OE1 GLN  146      27.851  80.253   0.083  1.00 47.57      A3
ATOM  1078 NE2 GLN  146      26.689  79.793  -1.692  1.00 47.50      A3
ATOM  1079 HE21 GLN  146      26.149  79.149  -2.190  1.00  0.00      A3
ATOM  1080 HE22 GLN  146      26.913  80.690  -2.021  1.00  0.00      A3
ATOM  1081 C   GLN  146      29.005  75.670   1.836  1.00 37.25      A3
ATOM  1082 O   GLN  146      29.634  75.093   0.950  1.00 38.28      A3
ATOM  1083 N   ARG  147      29.511  75.775   3.054  1.00 36.37      A3
ATOM  1084 H   ARG  147      29.044  76.300   3.738  1.00  0.00      A3
ATOM  1085 CA  ARG  147      30.798  75.180   3.357  1.00 35.68      A3
ATOM  1086 CB  ARG  147      31.299  75.574   4.713  1.00 37.12      A3
ATOM  1087 CG  ARG  147      31.730  77.016   4.697  1.00 42.68      A3
ATOM  1088 CD  ARG  147      32.034  77.494   6.093  1.00 49.54      A3
ATOM  1089 NE  ARG  147      32.674  78.774   5.877  1.00 58.21      A3
ATOM  1090 HE  ARG  147      32.475  79.252   5.045  1.00  0.00      A3
ATOM  1091 CZ  ARG  147      33.519  79.373   6.742  1.00 62.77      A3
ATOM  1092 NH1 ARG  147      33.905  78.868   7.916  1.00 64.96      A3
ATOM  1093 HH11 ARG  147      34.545  79.379   8.510  1.00 0.00      A3
ATOM  1094 HH12 ARG  147      33.561  77.980   8.239  1.00  0.00      A3
ATOM  1095 NH2 ARG  147      33.960  80.584   6.403  1.00 64.80      A3
ATOM  1096 HH21 ARG  147      34.599  81.069   6.999  1.00  0.00      A3
ATOM  1097 HH22 ARG  147      33.665  80.996   5.541  1.00  0.00      A3
ATOM  1098 C   ARG  147      30.570  73.702   3.317  1.00 34.91      A3
ATOM  1099 O   ARG  147      31.233  73.050   2.539  1.00 34.56      A3
ATOM  1100 N   ALA  148      29.544  73.194   4.040  1.00 33.44      A3
ATOM  1101 H   ALA  148      28.926  73.818   4.482  1.00  0.00      A3
ATOM  1102 CA  ALA  148      29.358  71.754   4.172  1.00 33.92      A3
ATOM  1103 CB  ALA  148      28.217  71.426   5.154  1.00 34.85      A3
ATOM  1104 C   ALA  148      29.077  71.095   2.845  1.00 33.40      A3
ATOM  1105 O   ALA  148      29.765  70.141   2.457  1.00 34.41      A3
ATOM  1106 N   ALA  149      28.169  71.657   2.077  1.00 32.60      A3
ATOM  1107 H   ALA  149      27.662  72.424   2.411  1.00  0.00      A3
ATOM  1108 CA  ALA  149      27.890  71.134   0.757  1.00 32.70      A3
ATOM  1109 CB  ALA  149      26.595  71.774   0.299  1.00 31.51      A3
ATOM  1110 C   ALA  149      29.032  71.381  -0.258  1.00 33.75      A3
ATOM  1111 O   ALA  149      29.208  70.661  -1.264  1.00 34.49      A3
ATOM  1112 N   GLY  150      29.867  72.401  -0.052  1.00 34.58      A3
ATOM  1113 H   GLY  150      29.724  73.035   0.682  1.00  0.00      A3
ATOM  1114 CA  GLY  150      31.017  72.608  -0.913  1.00 31.79      A3
ATOM  1115 C   GLY  150      32.113  71.629  -0.478  1.00 31.91      A3
ATOM  1116 O   GLY  150      32.997  71.261  -1.265  1.00 31.77      A3
ATOM  1117 N   GLY  151      32.075  71.161   0.773  1.00 29.83      A3
ATOM  1118 H   GLY  151      31.412  71.524   1.394  1.00  0.00      A3
ATOM  1119 CA  GLY  151      33.018  70.166   1.243  1.00 32.16      A3
ATOM  1120 C   GLY  151      32.764  68.909   0.409  1.00 33.56      A3
```

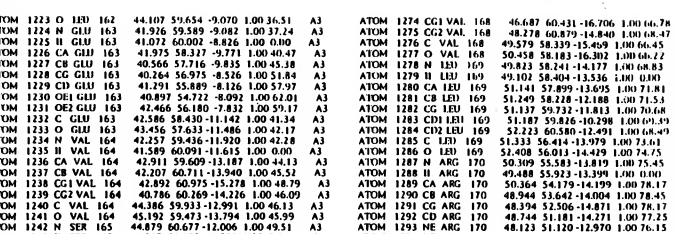

EP 0 612 846 B1

FIGURE 5

```
ATOM  1121  O  GLY  151      33.664  68.501  -0.349  1.00 35.66      A3
ATOM  1122  N  VAL  152      31.486  68.418   0.451  1.00 31.87      A3
ATOM  1123  H  VAL  152      30.867  68.906   1.040  1.00  0.00      A3
ATOM  1124  CA VAL  152      30.978  67.240  -0.275  1.00 29.61      A3
ATOM  1125  CB VAL  152      29.419  67.145  -0.125  1.00 27.63      A3
ATOM  1126  CG1 VAL  152      28.883  66.035  -0.976  1.00 27.37      A3
ATOM  1127  CG2 VAL  152      29.002  66.786   1.279  1.00 24.74      A3
ATOM  1128  C  VAL  152      31.351  67.294  -1.762  1.00 29.91      A3
ATOM  1129  O  VAL  152      31.805  66.329  -2.393  1.00 31.75      A3
ATOM  1130  N  LEU  153      31.236  68.452  -2.361  1.00 29.26      A3
ATOM  1131  H  LEU  153      30.881  69.219  -1.860  1.00  0.00      A3
ATOM  1132  CA LEU  153      31.559  68.607  -3.756  1.00 26.77      A3
ATOM  1133  CB LEU  153      30.881  69.858  -4.160  1.00 28.22      A3
ATOM  1134  CG LEU  153      29.943  69.894  -5.316  1.00 30.67      A3
ATOM  1135  CD1 LEU  153      28.580  69.281  -5.090  1.00 26.48      A3
ATOM  1136  CD2 LEU  153      29.741  71.365  -5.496  1.00 34.46      A3
ATOM  1137  C  LEU  153      33.032  68.628  -4.111  1.00 26.08      A3
ATOM  1138  O  LEU  153      33.419  68.187  -5.212  1.00 26.78      A3
ATOM  1139  N  VAL  154      33.902  69.180  -3.269  1.00 26.12      A3
ATOM  1140  H  VAL  154      33.589  69.557  -2.416  1.00  0.00      A3
ATOM  1141  CA VAL  154      35.330  69.259  -3.611  1.00 26.23      A3
ATOM  1142  CB VAL  154      36.057  70.299  -2.692  1.00 26.51      A3
ATOM  1143  CG1 VAL  154      37.578  70.188  -2.942  1.00 25.01      A3
ATOM  1144  CG2 VAL  154      35.528  71.728  -2.945  1.00 27.82      A3
ATOM  1145  C  VAL  154      35.933  67.850  -3.375  1.00 26.80      A3
ATOM  1146  O  VAL  154      36.678  67.363  -4.229  1.00 26.27      A3
ATOM  1147  N  ALA  155      35.635  67.241  -2.199  1.00 24.76      A3
ATOM  1148  H  ALA  155      35.084  67.758  -1.570  1.00  0.00      A3
ATOM  1149  CA ALA  155      36.095  65.940  -1.782  1.00 25.21      A3
ATOM  1150  CB ALA  155      35.463  65.572  -0.457  1.00 25.25      A3
ATOM  1151  C  ALA  155      35.708  64.946  -2.841  1.00 26.94      A3
ATOM  1152  O  ALA  155      36.594  64.288  -3.398  1.00 26.76      A3
ATOM  1153  N  SER  156      34.450  64.982  -3.282  1.00 29.96      A3
ATOM  1154  H  SER  156      33.790  65.577  -2.829  1.00  0.00      A3
ATOM  1155  CA SER  156      34.034  64.105  -4.354  1.00 32.17      A3
ATOM  1156  CB SER  156      32.531  64.314  -4.500  1.00 34.23      A3
ATOM  1157  OG SER  156      32.000  64.195  -5.879  1.00 39.35      A3
ATOM  1158  HG SER  156      31.120  63.815  -5.851  1.00  0.00      A3
ATOM  1159  C  SER  156      34.845  64.338  -5.632  1.00 33.46      A3
ATOM  1160  O  SER  156      35.411  63.380  -6.174  1.00 34.62      A3
ATOM  1161  N  HIS  157      35.054  65.576  -6.133  1.00 33.90      A3
ATOM  1162  H  HIS  157      34.771  66.349  -5.605  1.00  0.00      A3
ATOM  1163  CA HIS  157      35.821  65.773  -7.383  1.00 31.19      A3
ATOM  1164  CB HIS  157      35.707  67.209  -7.900  1.00 32.59      A3
ATOM  1165  CG HIS  157      34.369  67.449  -8.566  1.00 31.11      A3
ATOM  1166  CD2 HIS  157      34.127  67.394  -9.928  1.00 30.78      A3
ATOM  1167  ND1 HIS  157      33.223  67.666  -7.942  1.00 32.36      A3
ATOM  1168  HD1 HIS  157      33.080  67.773  -6.979  1.00  0.00      A3
ATOM  1169  CE1 HIS  157      32.293  67.732  -8.875  1.00 32.01      A3
ATOM  1170  NE2 HIS  157      32.838  67.571 -10.060  1.00 29.18      A3
ATOM  1171  HE2 HIS  157      32.327  67.621 -10.895  1.00  0.00      A4

ATOM  1172  C  HIS  157      37.291  65.476  -7.269  1.00 29.68      A4
ATOM  1173  O  HIS  157      37.950  65.059  -8.219  1.00 29.65      A3
ATOM  1174  N  LEU  158      37.801  65.669  -6.071  1.00 29.24      A3
ATOM  1175  H  LEU  158      37.213  65.901  -5.326  1.00  0.00      A3
ATOM  1176  CA LEU  158      39.216  65.479  -5.846  1.00 31.96      A3
ATOM  1177  CB LEU  158      39.609  65.949  -4.373  1.00 28.66      A3
ATOM  1178  CG LEU  158      41.008  65.751  -3.859  1.00 24.12      A3
ATOM  1179  CD1 LEU  158      41.990  66.378  -4.776  1.00 20.87      A3
ATOM  1180  CD2 LEU  158      41.099  66.330  -2.477  1.00 24.86      A3
ATOM  1181  C  LEU  158      29.468  63.994  -6.027  1.00 31.46      A4
ATOM  1182  O  LEU  158      40.298  63.609  -6.844  1.00 30.58      A3
ATOM  1183  N  GLN  159      38.652  63.225  -5.340  1.00 33.54      A3
ATOM  1184  H  GLN  159      38.011  63.676  -4.748  1.00  0.00      A3
ATOM  1185  CA GLN  159      38.594  61.792  -5.442  1.00 35.73      A3
ATOM  1186  CB GLN  159      37.308  61.492  -4.813  1.00 37.26      A3
ATOM  1187  CG GLN  159      37.064  60.063  -4.520  1.00 45.01      A3
ATOM  1188  CD GLN  159      37.755  59.611  -3.256  1.00 46.24      A3
ATOM  1189  OE1 GLN  159      38.142  58.443  -3.232  1.00 48.29      A3
ATOM  1190  NE2 GLN  159      37.936  60.456  -2.224  1.00 47.82      A3
ATOM  1191  HE21 GLN  159      37.575  61.364  -2.289  1.00  0.00      A3
ATOM  1192  HE22 GLN  159      38.412  60.101  -1.447  1.00  0.00      A3
ATOM  1193  C  GLN  159      38.686  61.381  -6.921  1.00 36.74      A3
ATOM  1194  O  GLN  159      39.632  60.690  -7.324  1.00 38.97      A3
ATOM  1195  N  SER  160      37.824  61.896  -7.796  1.00 35.48      A3
ATOM  1196  H  SER  160      37.142  62.540  -7.498  1.00  0.00      A3
ATOM  1197  CA SER  160      37.869  61.564  -9.203  1.00 34.96      A3
ATOM  1198  CB SER  160      36.645  62.100  -9.863  1.00 37.54      A3
ATOM  1199  OG SER  160      35.587  62.434  -8.942  1.00 44.81      A3
ATOM  1200  HG SER  160      35.340  61.689  -8.387  1.00  0.00      A3
ATOM  1201  C  SER  160      39.090  62.095  -9.922  1.00 31.65      A3
ATOM  1202  O  SER  160      39.605  61.382 -10.785  1.00 35.42      A3
ATOM  1203  N  PHE  161      39.615  63.293  -9.595  1.00 33.82      A3
ATOM  1204  H  PHE  161      39.203  63.796  -8.864  1.00  0.00      A3
ATOM  1205  CA PHE  161      40.820  63.826 -10.218  1.00 31.71      A3
ATOM  1206  CB PHE  161      41.110  65.254  -9.629  1.00 28.28      A3
ATOM  1207  CG PHE  161      42.455  65.881 -10.062  1.00 24.92      A3
ATOM  1208  CD1 PHE  161      42.696  66.228 -11.389  1.00 22.98      A3
ATOM  1209  CD2 PHE  161      43.464  66.021  -9.135  1.00 23.63      A3
ATOM  1210  CE1 PHE  161      43.941  66.695 -11.767  1.00 21.06      A3
ATOM  1211  CE2 PHE  161      44.701  66.495  -9.528  1.00 20.28      A3
ATOM  1212  CZ  PHE  161      44.939  66.826 -10.832  1.00 17.01      A3
ATOM  1213  C  PHE  161      42.008  62.907  -9.943  1.00 31.77      A3
ATOM  1214  O  PHE  161      42.786  62.575 -10.845  1.00 32.65      A3
ATOM  1215  N  LEU  162      42.117  62.434  -8.690  1.00 31.67      A3
ATOM  1216  H  LEU  162      41.420  62.691  -8.054  1.00  0.00      A4
ATOM  1217  CA LEU  162      43.186  61.574  -8.232  1.00 31.29      A3
ATOM  1218  CB LEU  162      43.204  61.433  -6.743  1.00 25.80      A3
ATOM  1219  CG LEU  162      43.693  62.674  -6.003  1.00 26.02      A4
ATOM  1220  CD1 LEU  162      43.594  62.455  -4.516  1.00 25.24      A4
ATOM  1221  CD2 LEU  162      45.107  62.994  -6.415  1.00 27.04      A3
ATOM  1222  C  LEU  162      43.061  60.212  -8.813  1.00 34.23      A3
```

FIGURE 5



```
ATOM  1223 O   LEU  162     44.107  59.654  -9.070  1.00 36.51      A3
ATOM  1224 N   GLU  163     41.926  59.589  -9.082  1.00 37.24      A3
ATOM  1225 H   GLU  163     41.072  60.002  -8.826  1.00  0.00      A3
ATOM  1226 CA  GLU  163     41.975  58.327  -9.771  1.00 40.47      A3
ATOM  1227 CB  GLU  163     40.566  57.716  -9.835  1.00 45.38      A3
ATOM  1228 CG  GLU  163     40.264  56.975  -8.526  1.00 51.84      A3
ATOM  1229 CD  GLU  163     41.291  55.889  -8.126  1.00 57.97      A3
ATOM  1230 OE1 GLU  163     40.897  54.722  -8.092  1.00 62.01      A3
ATOM  1231 OE2 GLU  163     42.466  56.180  -7.832  1.00 59.17      A3
ATOM  1232 C   GLU  163     42.586  58.430 -11.142  1.00 41.34      A3
ATOM  1233 O   GLU  163     43.456  57.633 -11.486  1.00 42.17      A3
ATOM  1234 N   VAL  164     42.257  59.436 -11.920  1.00 42.28      A3
ATOM  1235 H   VAL  164     41.589  60.091 -11.615  1.00  0.00      A3
ATOM  1236 CA  VAL  164     42.911  59.609 -13.187  1.00 44.13      A3
ATOM  1237 CB  VAL  164     42.207  60.711 -13.940  1.00 45.52      A3
ATOM  1238 CG1 VAL  164     42.892  60.975 -15.278  1.00 48.79      A3
ATOM  1239 CG2 VAL  164     40.786  60.269 -14.226  1.00 46.09      A3
ATOM  1240 C   VAL  164     44.386  59.933 -12.991  1.00 46.13      A3
ATOM  1241 O   VAL  164     45.192  59.473 -13.794  1.00 45.99      A3
ATOM  1242 N   SER  165     44.879  60.677 -12.006  1.00 49.51      A3
ATOM  1243 H   SER  165     44.287  61.173 -11.396  1.00  0.00      A3
ATOM  1244 CA  SER  165     46.325  60.845 -11.895  1.00 53.44      A3
ATOM  1245 CB  SER  165     46.715  61.796 -10.775  1.00 54.77      A3
ATOM  1246 OG  SER  165     46.049  61.618  -9.530  1.00 59.99      A3
ATOM  1247 HG  SER  165     45.997  60.694  -9.261  1.00  0.00      A3
ATOM  1248 C   SER  165     46.958  59.501 -11.610  1.00 55.15      A3
ATOM  1249 O   SER  165     48.028  59.227 -12.148  1.00 55.02      A3
ATOM  1250 N   TYR  166     46.239  58.645 -10.900  1.00 58.57      A3
ATOM  1251 H   TYR  166     45.374  58.948 -10.549  1.00  0.00      A3
ATOM  1252 CA  TYR  166     46.617  57.273 -10.625  1.00 61.42      A3
ATOM  1253 CB  TYR  166     45.543  56.653  -9.680  1.00 64.05      A3
ATOM  1254 CG  TYR  166     45.502  55.138  -9.682  1.00 69.00      A3
ATOM  1255 CD1 TYR  166     44.389  54.501 -10.185  1.00 71.64      A3
ATOM  1256 CE1 TYR  166     44.367  53.130 -10.283  1.00 73.15      A3
ATOM  1257 CD2 TYR  166     46.594  54.409  -9.253  1.00 71.27      A3
ATOM  1258 CE2 TYR  166     46.584  53.040  -9.346  1.00 72.92      A3
ATOM  1259 CZ  TYR  166     45.468  52.417  -9.862  1.00 75.71      A3
ATOM  1260 OH  TYR  166     45.474  51.038 -10.016  1.00 80.61      A3
ATOM  1261 HH  TYR  166     44.571  50.736 -10.134  1.00  0.00      A3
ATOM  1262 C   TYR  166     46.712  56.567 -11.987  1.00 62.34      A3
ATOM  1263 O   TYR  166     47.766  55.981 -12.282  1.00 63.25      A3
ATOM  1264 N   ALA  167     45.727  56.622 -12.884  1.00 61.27      A3
ATOM  1265 H   ALA  167     44.893  57.089 -12.678  1.00  0.00      A3
ATOM  1266 CA  ALA  167     45.933  55.982 -14.159  1.00 61.47      A3
ATOM  1267 CB  ALA  167     44.608  55.904 -14.904  1.00 60.98      A3
ATOM  1268 C   ALA  167     46.982  56.694 -15.020  1.00 62.19      A3
ATOM  1269 O   ALA  167     47.719  56.000 -15.734  1.00 62.63      A3
ATOM  1270 N   VAL  168     47.210  58.011 -14.991  1.00 63.37      A3
ATOM  1271 H   VAL  168     46.756  58.570 -14.330  1.00  0.00      A3
ATOM  1272 CA  VAL  168     48.174  58.593 -15.923  1.00 65.62      A3
ATOM  1273 CB  VAL  168     48.061  60.121 -16.131  1.00 66.30      A3
ATOM  1274 CG1 VAL  168     46.687  60.431 -16.706  1.00 66.78      A3
ATOM  1275 CG2 VAL  168     48.278  60.879 -14.840  1.00 68.47      A3
ATOM  1276 C   VAL  168     49.579  58.339 -15.469  1.00 66.45      A3
ATOM  1277 O   VAL  168     50.458  58.183 -16.302  1.00 66.22      A3
ATOM  1278 N   LEU  169     49.823  58.241 -14.177  1.00 68.83      A3
ATOM  1279 H   LEU  169     49.102  58.404 -13.536  1.00  0.00      A3
ATOM  1280 CA  LEU  169     51.141  57.899 -13.695  1.00 71.81      A3
ATOM  1281 CB  LEU  169     51.249  58.228 -12.188  1.00 71.53      A3
ATOM  1282 CG  LEU  169     51.137  59.732 -11.813  1.00 70.68      A3
ATOM  1283 CD1 LEU  169     51.187  59.826 -10.298  1.00 69.89      A3
ATOM  1284 CD2 LEU  169     52.223  60.580 -12.491  1.00 68.49      A3
ATOM  1285 C   LEU  169     51.333  56.414 -13.979  1.00 73.61      A3
ATOM  1286 O   LEU  169     52.408  56.013 -14.429  1.00 74.75      A3
ATOM  1287 N   ARG  170     50.309  55.583 -13.819  1.00 75.45      A3
ATOM  1288 H   ARG  170     49.488  55.923 -13.399  1.00  0.00      A3
ATOM  1289 CA  ARG  170     50.364  54.179 -14.199  1.00 78.17      A3
ATOM  1290 CB  ARG  170     48.944  53.642 -14.004  1.00 78.45      A3
ATOM  1291 CG  ARG  170     48.394  52.506 -14.871  1.00 76.17      A3
ATOM  1292 CD  ARG  170     48.744  51.181 -14.271  1.00 77.25      A3
ATOM  1293 NE  ARG  170     48.123  51.120 -12.970  1.00 76.15      A3
ATOM  1294 HE  ARG  170     47.245  51.528 -12.824  1.00  0.00      A3
ATOM  1295 CZ  ARG  170     48.758  50.547 -11.970  1.00 76.14      A3
ATOM  1296 NH1 ARG  170     49.973  50.017 -12.112  1.00 76.84      A3
ATOM  1297 HH11 ARG  170     50.441  50.030 -12.994  1.00  0.00      A3
ATOM  1298 HH12 ARG  170     50.406  49.570 -11.329  1.00  0.00      A3
ATOM  1299 NH2 ARG  170     48.447  50.492 -10.696  1.00 77.02      A3
ATOM  1300 HH21 ARG  170     47.237  50.890 -10.714  1.00  0.00      A3
ATOM  1301 HH22 ARG  170     48.586  50.052 -10.023  1.00  0.00      A3
ATOM  1302 C   ARG  170     50.870  54.052 -15.647  1.00 79.84      A1
ATOM  1303 O   ARG  170     51.924  53.470 -15.908  1.00 80.07      A1
ATOM  1304 N   HIS  171     50.193  54.663 -16.611  1.00 81.38      A3
ATOM  1305 H   HIS  171     49.433  55.234 -16.359  1.00  0.00      A3
ATOM  1306 CA  HIS  171     50.663  54.597 -17.970  1.00 84.03      A1
ATOM  1307 CB  HIS  171     49.590  55.054 -18.902  1.00 86.82      A3
ATOM  1308 CG  HIS  171     48.496  54.037 -19.147  1.00 90.73      A3
ATOM  1309 CD2 HIS  171     47.467  53.765 -18.272  1.00 91.35      A3
ATOM  1310 ND1 HIS  171     48.308  53.301 -20.248  1.00 92.24      A3
ATOM  1311 HD1 HIS  171     48.887  53.287 -21.044  1.00  0.00      A3
ATOM  1312 CE1 HIS  171     47.204  52.605 -20.077  1.00 92.41      A3
ATOM  1313 NE2 HIS  171     46.711  52.892 -18.891  1.00 92.59      A3
ATOM  1314 HE2 HIS  171     45.884  52.511 -18.518  1.00  0.00      A1
ATOM  1315 C   HIS  171     51.907  55.446 -18.232  1.00 85.42      A3
ATOM  1316 O   HIS  171     52.440  55.352 -19.344  1.00 85.98      A1
ATOM  1317 N   LEU  172     52.359  56.307 -17.302  1.00 86.13      A3
ATOM  1318 H   LEU  172     51.870  56.411 -16.463  1.00  0.00      A3
ATOM  1319 CA  LEU  172     53.550  57.133 -17.496  1.00 86.02      A3
ATOM  1320 CB  LEU  172     53.500  58.357 -16.607  1.00 86.31      A3
ATOM  1321 CG  LEU  172     54.022  59.658 -17.203  1.00 87.48      A3
ATOM  1322 CD1 LEU  172     53.436  59.939 -18.596  1.00 87.68      A3
ATOM  1323 CD2 LEU  172     53.645  60.778 -16.251  1.00 87.95      A3
ATOM  1324 C   LEU  172     54.813  56.357 -17.180  1.00 85.92      A1
```

FIGURE 5

```
ATOM  1325  O  LEU  172      55.896  56.660 -17.692  1.00 86.23      A3
ATOM  1326  N  ALA  173      54.733  55.383 -16.282  1.00 85.49      A3
ATOM  1327  H  ALA  173      53.899  55.276 -15.769  1.00  0.00      A3
ATOM  1328  CA ALA  173      55.856  54.497 -16.087  1.00 85.65      A3
ATOM  1329  CB ALA  173      56.602  54.859 -14.809  1.00 85.01      A3
ATOM  1330  C  ALA  173      55.330  53.073 -16.008  1.00 86.54      A3
ATOM  1331  OT1 ALA  173      55.585  52.347 -16.971  1.00 87.21      A3
ATOM  1332  OT2 ALA  173      54.650  52.707 -15.036  1.00 87.31      A3
ATOM  1333  CB LEU  210      45.234  42.591  25.453  1.00 52.47      B1
ATOM  1334  CG LEU  210      43.799  42.058  25.547  1.00 51.68      B1
ATOM  1335  CD1 LEU  210      43.123  42.562  26.804  1.00 53.37      B1
ATOM  1336  CD2 LEU  210      43.050  42.453  24.303  1.00 51.37      B1
ATOM  1337  C  LEU  210      46.770  44.374  24.596  1.00 50.98      B1
ATOM  1338  O  LEU  210      46.475  45.267  23.790  1.00 51.76      B1
ATOM  1339  1HT1 LEU  210      44.382  44.922  24.423  1.00  0.00      B1
ATOM  1340  1HT2 LEU  210      45.157  45.974  25.414  1.00  0.00      B1
ATOM  1341  N  LEU  210      44.705  45.041  25.406  1.00 53.59      B1
ATOM  1342  HT3 LEU  210      43.855  45.012  25.997  1.00  0.00      B1
ATOM  1343  CA LEU  210      45.730  44.038  25.676  1.00 52.35      B1
ATOM  1344  N  PRO  211      47.974  43.825  24.494  1.00 49.35      B1
ATOM  1345  CD PRO  211      48.621  43.024  25.532  1.00 49.52      B1
ATOM  1346  CA PRO  211      48.895  44.191  23.419  1.00 49.04      B1
ATOM  1347  CB PRO  211      50.209  43.571  23.865  1.00 49.02      B1
ATOM  1348  CG PRO  211      49.794  42.438  24.783  1.00 49.77      B1
ATOM  1349  C  PRO  211      48.543  43.864  21.965  1.00 48.88      B1
ATOM  1350  O  PRO  211      47.872  42.896  21.678  1.00 49.05      B1
ATOM  1351  N  GLN  212      49.032  44.675  21.051  1.00 46.52      B1
ATOM  1352  H  GLN  212      49.506  45.478  21.349  1.00  0.00      B1
ATOM  1353  CA GLN  212      48.839  44.461  19.641  1.00 47.47      B1
ATOM  1354  CB GLN  212      49.533  45.522  18.849  1.00 46.81      B1
ATOM  1355  CG GLN  212      48.482  46.139  17.999  1.00 49.55      B1
ATOM  1356  CD GLN  212      49.024  46.703  16.709  1.00 54.21      B1
ATOM  1357  OE1 GLN  212      48.429  47.672  16.232  1.00 57.72      B1
ATOM  1358  NE2 GLN  212      50.086  46.176  16.154  1.00 52.39      B1
ATOM  1359  HE21 GLN  212      50.530  45.383  16.430  1.00  0.00      B1
ATOM  1360  HE22 GLN  212      50.341  46.625  15.244  1.00  0.00      B1
ATOM  1361  C  GLN  212      49.390  43.133  19.185  1.00 44.79      B1
ATOM  1362  O  GLN  212      48.959  42.520  18.208  1.00 44.01      B1
ATOM  1363  N  SER  213      50.401  42.671  19.893  1.00 44.72      B1
ATOM  1364  H  SER  213      50.730  43.115  20.698  1.00  0.00      B1
ATOM  1365  CA SER  213      51.025  41.424  19.521  1.00 43.76      B1
ATOM  1366  CB SER  213      52.220  41.124  20.354  1.00 45.29      B1
ATOM  1367  OG SER  213      51.802  41.455  21.681  1.00 52.50      B1
ATOM  1368  HG SER  213      52.479  41.127  22.288  1.00  0.00      B1
ATOM  1369  C  SER  213      50.014  40.376  19.784  1.00 40.92      B1
ATOM  1370  O  SER  213      49.964  39.492  18.947  1.00 43.32      B1
ATOM  1371  N  PHE  214      49.242  40.571  20.876  1.00 38.86      B1
ATOM  1372  H  PHE  214      49.414  41.370  21.410  1.00  0.00      B1
ATOM  1373  CA PHE  214      48.710  39.664  21.336  1.00 37.40      B1
ATOM  1374  CB PHE  214      47.568  40.064  22.634  1.00 37.45      B1
ATOM  1375  CG PHE  214      46.494  39.080  23.035  1.00 41.01      B1
ATOM  1376  CD1 PHE  214      45.176  39.459  23.044  1.00 42.77      B1
ATOM  1377  CD2 PHE  214      46.818  37.794  23.400  1.00 42.02      B1
ATOM  1378  CE1 PHE  214      44.197  38.554  23.423  1.00 41.82      B1
ATOM  1379  CE2 PHE  214      45.834  36.898  23.776  1.00 41.70      B1
ATOM  1380  CZ  PHE  214      44.519  37.277  23.791  1.00 41.05      B1
ATOM  1381  C  PHE  214      47.109  39.656  20.321  1.00 36.54      B1
ATOM  1382  O  PHE  214      46.735  38.566  19.889  1.00 37.99      B1
ATOM  1383  N  LEU  215      46.616  40.812  19.893  1.00 33.27      B1
ATOM  1384  H  LEU  215      47.008  41.642  20.238  1.00  0.00      B1
ATOM  1385  CA LEU  215      45.504  40.864  18.966  1.00 30.38      B1
ATOM  1386  CB LEU  215      45.099  42.282  18.701  1.00 31.82      B1
ATOM  1387  CG LEU  215      43.857  42.530  17.893  1.00 32.78      B1
ATOM  1388  CD1 LEU  215      42.727  41.963  18.737  1.00 32.95      B1
ATOM  1389  CD2 LEU  215      43.688  44.011  17.508  1.00 28.93      B1
ATOM  1390  C  LEU  215      45.811  40.232  17.648  1.00 29.57      B1
ATOM  1391  O  LEU  215      44.922  39.632  17.055  1.00 31.28      B1
ATOM  1392  N  LEU  216      47.031  40.379  17.155  1.00 29.44      B1
ATOM  1393  H  LEU  216      47.677  40.935  17.646  1.00  0.00      B1
ATOM  1394  CA LEU  216      47.465  39.790  15.893  1.00 29.89      B1
ATOM  1395  CB LEU  216      48.791  40.450  15.472  1.00 28.61      B1
ATOM  1396  CG LEU  216      48.682  41.877  14.939  1.00 26.83      B1
ATOM  1397  CD1 LEU  216      49.925  42.558  15.344  1.00 28.57      B1
ATOM  1398  CD2 LEU  216      48.446  41.950  13.452  1.00 24.09      B1
ATOM  1399  C  LEU  216      47.613  38.274  16.062  1.00 31.15      B1
ATOM  1400  O  LEU  216      47.328  37.514  15.138  1.00 29.20      B1
ATOM  1401  N  LYS  217      47.999  37.826  17.261  1.00 32.50      B1
ATOM  1402  H  LYS  217      48.305  38.482  17.926  1.00  0.00      B1
ATOM  1403  CA LYS  217      48.067  36.439  17.592  1.00 34.90      B1
ATOM  1404  CB LYS  217      48.645  36.280  19.002  1.00 38.07      B1
ATOM  1405  CG LYS  217      49.394  34.978  19.109  1.00 45.25      B1
ATOM  1406  CD LYS  217      49.714  34.491  20.521  1.00 53.27      B1
ATOM  1407  CE LYS  217      50.229  33.024  20.297  1.00 59.04      B1
ATOM  1408  NZ LYS  217      50.213  32.135  21.467  1.00 62.10      B1
ATOM  1409  1HZ1 LYS  217      49.239  32.056  21.824  1.00  0.00      B1
ATOM  1410  1HZ2 LYS  217      50.830  32.515  22.214  1.00  0.00      B1
ATOM  1411  1HZ3 LYS  217      50.554  31.195  21.179  1.00  0.00      B1
ATOM  1412  C  LYS  217      46.617  35.950  17.546  1.00 36.71      B1
ATOM  1413  O  LYS  217      46.311  34.933  16.886  1.00 34.58      B1
ATOM  1414  N  CYS  218      45.664  36.638  18.177  1.00 34.86      B1
ATOM  1415  H  CYS  218      45.907  37.388  18.751  1.00  0.00      B1
ATOM  1416  CA CYS  218      44.277  36.238  18.026  1.00 34.61      B1
ATOM  1417  CB CYS  218      43.430  37.175  18.846  1.00 33.21      B1
ATOM  1418  SG CYS  218      43.856  36.710  20.515  1.00 35.92      B1
ATOM  1419  C  CYS  218      43.766  36.189  16.652  1.00 32.89      B1
ATOM  1420  O  CYS  218      43.155  35.169  16.323  1.00 34.71      B1
ATOM  1421  N  LEU  219      44.035  37.169  15.777  1.00 29.52      B1
ATOM  1422  H  LEU  219      44.512  37.960  16.104  1.00  0.00      B1
ATOM  1423  CA LEU  219      43.614  37.119  14.393  1.00 27.44      B1
ATOM  1424  CB LEU  219      44.116  38.412  13.727  1.00 26.24      B1
ATOM  1425  CG LEU  219      43.884  38.768  12.241  1.00 25.07      B1
ATOM  1426  CD1 LEU  219      42.402  38.975  11.996  1.00 26.24      B1
```

FIGURE 5

```
ATOM  1427 CD2 LEU  219      44.563 ?, .051  11.882  1.00 22.10      B1
ATOM  1428 C   LEU  219      44.121  35.867  12.634  1.00 28.24      B1
ATOM  1429 O   LEU  219      43.373  35.204  12.889  1.00 27.12      B1
ATOM  1430 N   GLU  220      45.399  35.499  13.795  1.00 28.06      B1
ATOM  1431 H   GLU  220      45.957  35.974  14.448  1.00  0.00      B1
ATOM  1432 CA  GLU  220      45.963  34.411  13.048  1.00 28.38      B1
ATOM  1433 CB  GLU  220      47.376  34.198  13.469  1.00 34.25      B1
ATOM  1434 CG  GLU  220      48.049  33.079  12.666  1.00 46.36      B1
ATOM  1435 CD  GLU  220      49.545  32.794  12.907  1.00 55.51      B1
ATOM  1436 OE1 GLU  220      50.313  32.133  12.021  1.00 58.95      B1
ATOM  1437 OE2 GLU  220      50.144  33.213  13.930  1.00 60.41      B1
ATOM  1438 C   GLU  220      45.134  33.093  13.354  1.00 27.30      B1
ATOM  1439 O   GLU  220      44.662  32.524  12.437  1.00 27.08      B1
ATOM  1440 N   GLN  221      44.866  33.023  14.642  1.00 25.42      B1
ATOM  1441 H   GLN  221      45.229  33.687  15.268  1.00  0.00      B1
ATOM  1442 CA  GLN  221      44.074  31.940  15.176  1.00 26.28      B1
ATOM  1443 CB  GLN  221      44.143  31.927  16.691  1.00 26.78      B1
ATOM  1444 CG  GLN  221      45.555  31.456  17.011  1.00 29.19      B1
ATOM  1445 CD  GLN  221      45.752  31.067  18.442  1.00 31.98      B1
ATOM  1446 OE1 GLN  221      46.472  30.162  18.808  1.00 35.98      B1
ATOM  1447 NE2 GLN  221      45.110  31.736  19.347  1.00 39.31      B1
ATOM  1448 HE21 GLN  221      45.263  31.423  20.246  1.00  0.00      B1
ATOM  1449 HE22 GLN  221      44.571  32.514  19.111  1.00  0.00      B1
ATOM  1450 C   GLN  221      42.615  31.925  14.789  1.00 26.21      B1
ATOM  1451 O   GLN  221      42.186  30.896  14.269  1.00 30.69      B1
ATOM  1452 N   VAL  222      41.814  32.962  14.984  1.00 23.63      B1
ATOM  1453 H   VAL  222      42.199  33.746  15.426  1.00  0.00      B1
ATOM  1454 CA  VAL  222      40.429  33.034  14.537  1.00 21.92      B1
ATOM  1455 CB  VAL  222      39.934  34.442  14.793  1.00 21.36      B1
ATOM  1456 CG1 VAL  222      38.706  34.831  14.027  1.00 17.72      B1
ATOM  1457 CG2 VAL  222      39.671  34.496  16.257  1.00 20.95      B1
ATOM  1458 C   VAL  222      40.374  32.707  13.066  1.00 22.55      B1
ATOM  1459 O   VAL  222      39.473  32.013  12.632  1.00 23.72      B1
ATOM  1460 N   ARG  223      41.341  33.120  12.283  1.00 23.95      B1
ATOM  1461 H   ARG  223      42.099  33.614  12.666  1.00  0.00      B1
ATOM  1462 CA  ARG  223      41.309  32.939  10.844  1.00 27.19      B1
ATOM  1463 CB  ARG  223      42.294  33.935  10.283  1.00 29.26      B1
ATOM  1464 CG  ARG  223      42.102  34.364  8.869  1.00 35.23      B1
ATOM  1465 CD  ARG  223      42.880  33.487  7.929  1.00 41.88      B1
ATOM  1466 NE  ARG  223      41.972  32.676  7.096  1.00 47.42      B1
ATOM  1467 HE  ARG  223      41.451  31.953  7.502  1.00  0.00      B1
ATOM  1468 CZ  ARG  223      41.875  32.896  5.784  1.00 46.15      B1
ATOM  1469 NH1 ARG  223      42.575  33.837  5.246  1.00 49.54      B1
ATOM  1470 HH11 ARG  223      42.522  33.989  4.259  1.00  0.00      B1
ATOM  1471 HH12 ARG  223      43.156  34.428  5.805  1.00  0.00      B1
ATOM  1472 NH2 ARG  223      41.178  32.161  4.952  1.00 45.74      B1
ATOM  1473 HH21 ARG  223      40.697  31.353  5.290  1.00  0.00      B1
ATOM  1474 HH22 ARG  223      41.154  32.399  3.980  1.00  0.00      B1
ATOM  1475 C   ARG  223      41.624  31.492  10.430  1.00 29.13      B1
ATOM  1476 O   ARG  223      41.181  30.987  9.376  1.00 29.32      B1
ATOM  1477 N   LYS  224      42.413  30.791  11.259  1.00 29.17      B1
ATOM  1478     LYS  224      42.791  31.235  12.048  1.00  0.00      B1
ATOM  1479 CA  LYS  224      42.714  29.411  10.994  1.00 27.76      B1
ATOM  1480 CB  LYS  224      43.922  29.085  11.818  1.00 30.07      B1
ATOM  1481 CG  LYS  224      44.372  27.660  11.706  1.00 36.70      B1
ATOM  1482 CD  LYS  224      45.829  27.544  12.127  1.00 41.68      B1
ATOM  1483 CE  LYS  224      46.303  26.478  11.131  1.00 44.18      B1
ATOM  1484 NZ  LYS  224      47.750  26.492  10.913  1.00 53.57      B1
ATOM  1485 HZ1 LYS  224      48.230  26.241  11.801  1.00  0.00      B1
ATOM  1486 HZ2 LYS  224      48.057  27.436  10.606  1.00  0.00      B1
ATOM  1487 HZ3 LYS  224      47.998  25.792  10.183  1.00  0.00      B1
ATOM  1488 C   LYS  224      41.464  28.598  11.347  1.00 26.27      B1
ATOM  1489 O   LYS  224      40.970  27.810  10.510  1.00 24.82      B1
ATOM  1490 N   ILE  225      40.892  28.835  12.547  1.00 24.75      B1
ATOM  1491 H   ILE  225      41.308  29.487  13.151  1.00  0.00      B1
ATOM  1492 CA  ILE  225      39.656  28.147  12.943  1.00 23.33      B1
ATOM  1493 CB  ILE  225      39.146  28.622  14.296  1.00 18.08      B1
ATOM  1494 CG2 ILE  225      37.874  27.872  14.577  1.00 15.43      B1
ATOM  1495 CG1 ILE  225      40.161  28.400  15.380  1.00 13.58      B1
ATOM  1496 CD ILE  225      39.787  28.967  16.749  1.00 13.55      B1
ATOM  1497 C   ILE  225      38.594  28.437  11.889  1.00 27.28      B1
ATOM  1498 O   ILE  225      37.978  27.492  11.400  1.00 31.49      B1
ATOM  1499 N   GLN  226      38.396  29.677  11.402  1.00 29.69      B1
ATOM  1500 H   GLN  226      38.894  30.413  11.803  1.00  0.00      B1
ATOM  1501 CA  GLN  226      37.450  29.969  10.313  1.00 29.12      B1
ATOM  1502 CB  GLN  226      37.366  31.438  9.962  1.00 32.26      B1
ATOM  1503 CG  GLN  226      36.682  32.156  11.108  1.00 36.28      B1
ATOM  1504 CD  GLN  226      36.429  33.613  10.816  1.00 37.88      B1
ATOM  1505 OE1 GLN  226      37.158  34.281  10.076  1.00 36.34      B1
ATOM  1506 NE2 GLN  226      35.359  34.114  11.421  1.00 39.62      B1
ATOM  1507 HE21 GLN  226      34.823  33.501  11.971  1.00  0.00      B1
ATOM  1508 HE22 GLN  226      35.153  35.057  11.287  1.00  0.00      B1
ATOM  1509 C   GLN  226      37.714  29.295  9.007  1.00 26.82      B1
ATOM  1510 O   GLN  226      36.775  28.887  8.325  1.00 27.45      B1
ATOM  1511 N   GLY  227      38.940  29.186  8.570  1.00 26.55      B1
ATOM  1512 H   GLY  227      39.688  29.612  9.043  1.00  0.00      B1
ATOM  1513 CA  GLY  227      39.195  28.427  7.348  1.00 27.27      B1
ATOM  1514 C   GLY  227      38.832  26.949  7.574  1.00 27.65      B1
ATOM  1515 O   GLY  227      38.287  26.291  6.656  1.00 26.79      B1
ATOM  1516 N   ASP  228      39.025  26.429  8.819  1.00 27.03      B1
ATOM  1517 H   ASP  228      39.460  26.957  9.523  1.00  0.00      B1
ATOM  1518 CA  ASP  228      38.618  25.038  9.052  1.00 28.20      B1
ATOM  1519 CB  ASP  228      38.986  24.492  10.391  1.00 26.04      B1
ATOM  1520 CG  ASP  228      40.477  24.554  10.774  1.00 24.88      B1
ATOM  1521 OD1 ASP  228      40.627  24.521  11.977  1.00 23.17      B1
ATOM  1522 OD2 ASP  228      41.302  24.637  9.912  1.00 23.32      B1
ATOM  1523 C   ASP  228      37.120  24.830  8.992  1.00 27.21      B1
ATOM  1524 O   ASP  228      36.662  23.900  8.336  1.00 27.07      B1
ATOM  1525 N   GLY  229      36.390  25.739  9.639  1.00 26.74      B1
ATOM  1526 H   GLY  229      36.861  26.444  10.134  1.00  0.00      B1
ATOM  1527 CA  GLY  229      34.946  25.723  9.673  1.00 25.87      B1
ATOM  1528 C   GLY  229      34.393  25.825  8.274  1.00 24.95      B1
```

FIGURE 5

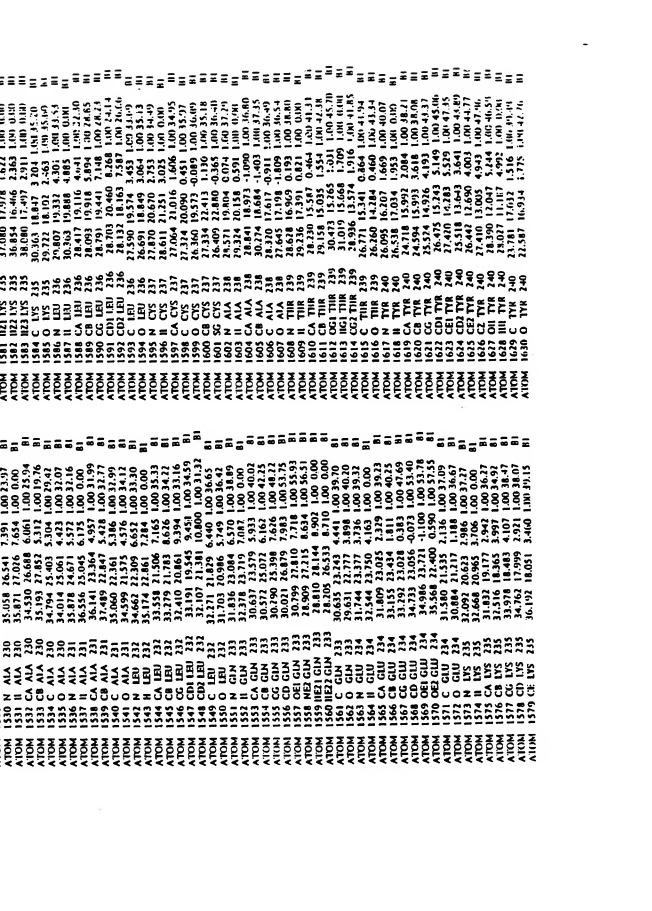


FIGURE 5

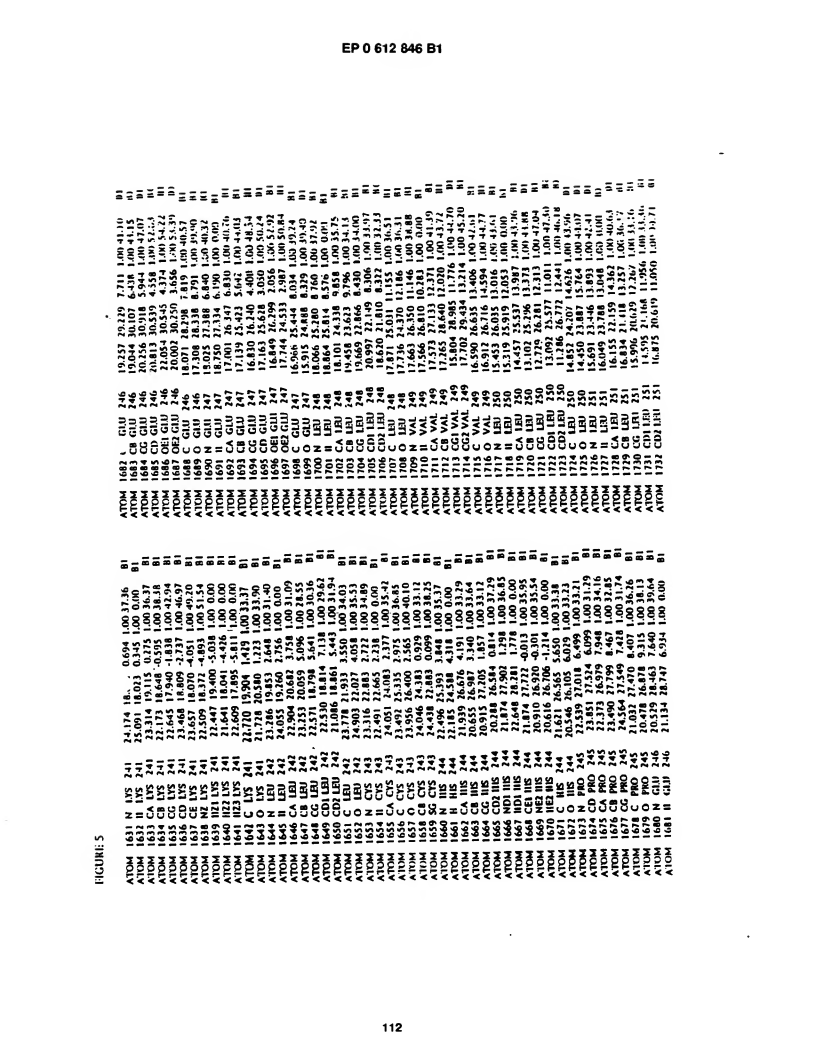


FIGURE 5

```
ATOM  1733 C  LEU 251     17.104  22.372  15.493  1.00 42.78      B1
ATOM  1734 O  LEU 251     17.124  21.554  16.395  1.00 45.44      B1
ATOM  1735 N  GLY 252     17.826  23.477  15.610  1.00 44.86      B1
ATOM  1736 H  GLY 252     17.750  24.160  14.910  1.00  0.00      B1
ATOM  1737 CA GLY 252     18.734  23.711  16.719  1.00 46.68      B1
ATOM  1738 C  GLY 252     18.071  23.596  18.067  1.00 49.18      B1
ATOM  1739 O  GLY 252     18.709  23.318  19.077  1.00 49.23      B1
ATOM  1740 N  HIS 253     16.756  23.787  18.046  1.00 53.74      B1
ATOM  1741 H  HIS 253     16.358  24.055  17.190  1.00  0.00      B1
ATOM  1742 CA HIS 253     15.859  23.649  19.197  1.00 57.46      B1
ATOM  1743 CB HIS 253     14.468  24.157  18.764  1.00 62.93      B1
ATOM  1744 CG HIS 253     13.212  23.813  19.577  1.00 68.75      B1
ATOM  1745 CD2 HIS 253     12.031  24.529  19.414  1.00 71.00      B1
ATOM  1746 ND1 HIS 253     12.980  22.854  20.479  1.00 70.67      B1
ATOM  1747 HD1 HIS 253     13.627  22.193  20.830  1.00  0.00      B1
ATOM  1748 CE1 HIS 253     11.723  22.966  20.845  1.00 73.40      B1
ATOM  1749 NE2 HIS 253.    11.156  23.973  20.204  1.00 72.91      B1
ATOM  1750 HE2 HIS 253     10.218  24.260  20.311  1.00  0.00      B1
ATOM  1751 C  HIS 253     15.771  22.209  19.691  1.00 56.06      B1
ATOM  1752 O  HIS 253     15.880  21.837  20.857  1.00 56.17      B1
ATOM  1753 N  SER 254     15.395  21.435  18.724  1.00 53.46      B1
ATOM  1754 H  SER 254     15.278  21.783  17.813  1.00  0.00      B1
ATOM  1755 CA SER 254     15.177  20.034  18.898  1.00 52.61      B1
ATOM  1756 CB SER 254     14.613  19.595  17.576  1.00 53.04      B1
ATOM  1757 OG SER 254     13.793  20.686  17.158  1.00 56.04      B1
ATOM  1758 HG SER 254     13.369  20.467  16.319  1.00  0.00      B1
ATOM  1759 C  SER 254     16.517  19.386  19.275  1.00 51.48      B1
ATOM  1760 O  SER 254     16.596  18.639  20.245  1.00 51.90      B1
ATOM  1761 N  LEU 255     17.577  19.790  18.562  1.00 49.31      B1
ATOM  1762 H  LEU 255     17.430  20.480  17.889  1.00  0.00      B1
ATOM  1763 CA LEU 255     18.913  19.272  18.723  1.00 46.02      B1
ATOM  1764 CB LEU 255     19.706  19.723  17.537  1.00 44.66      B1
ATOM  1765 CG LEU 255     19.362  18.968  16.274  1.00 44.51      B1
ATOM  1766 CD1 LEU 255     19.810  19.679  15.006  1.00 43.16      B1
ATOM  1767 CD2 LEU 255     19.969  17.604  16.456  1.00 44.67      B1
ATOM  1768 C  LEU 255     19.536  19.718  20.012  1.00 46.56      B1
ATOM  1769 O  LEU 255     20.565  19.174  20.440  1.00 46.82      B1
ATOM  1770 N  GLY 256     18.918  20.759  20.581  1.00 45.93      B1
ATOM  1771 H  GLY 256     18.210  21.225  20.101  1.00  0.00      B1
ATOM  1772 CA GLY 256     19.277  21.273  21.890  1.00 46.68      B1
ATOM  1773 C  GLY 256     20.669  21.866  21.970  1.00 47.28      B1
ATOM  1774 O  GLY 256     21.273  21.844  23.056  1.00 49.64      B1
ATOM  1775 N  ILE 257     21.143  22.441  20.849  1.00 45.74      B1
ATOM  1776 H  ILE 257     20.497  22.589  20.128  1.00  0.00      B1
ATOM  1777 CA ILE 257     22.481  23.017  20.726  1.00 43.64      B1
ATOM  1778 CB ILE 257     22.684  23.363  19.257  1.00 42.54      B1
ATOM  1779 CG2 ILE 257     23.988  24.110  19.073  1.00 41.05      B1
ATOM  1780 CG1 ILE 257     22.694  22.088  18.437  1.00 40.55      B1
ATOM  1781 CD ILE 257     22.452  22.468  16.970  1.00 39.49      B1
ATOM  1782 C  ILE 257     22.559  24.246  21.616  1.00 43.27      B1
ATOM  1783 O  ILE 257     21.706  25.110  21.450  1.00 43.22      B1

ATOM  1784 N  PRO 258     23.441  24.392  22.608  1.00 43.05      B1
ATOM  1785 CD PRO 258     24.433  23.321  23.296  1.00 43.29      B1
ATOM  1786 CA PRO 258     23.559  25.616  23.360  1.00 43.82      B1
ATOM  1787 CB PRO 258     24.295  25.236  24.612  1.00 41.97      B1
ATOM  1788 CG PRO 258     25.107  24.064  24.186  1.00 41.79      B1
ATOM  1789 C  PRO 258     24.252  26.703  22.555  1.00 46.06      B1
ATOM  1790 O  PRO 258     24.983  26.513  21.560  1.00 46.59      B1
ATOM  1791 N  TRP 259     23.996  27.887  23.106  1.00 46.75      B1
ATOM  1792 H  TRP 259     23.588  27.921  23.994  1.00  0.00      B1
ATOM  1793 CA TRP 259     24.427  29.143  22.517  1.00 45.77      B1
ATOM  1794 CB TRP 259     23.213  30.071  22.397  1.00 46.60      B1
ATOM  1795 CG TRP 259     23.556  31.372  21.749  1.00 47.51      B1
ATOM  1796 CD2 TRP 259     23.860  31.525  20.430  1.00 47.83      B1
ATOM  1797 CE2 TRP 259     24.154  32.888  20.392  1.00 48.47      B1
ATOM  1798 CE3 TRP 259     23.940  30.745  19.290  1.00 47.59      B1
ATOM  1799 CD1 TRP 259     23.639  32.520  22.493  1.00 48.60      B1
ATOM  1800 NE1 TRP 259     24.013  33.421  21.628  1.00 48.27      B1
ATOM  1801 HE1 TRP 259     24.224  34.344  21.870  1.00  0.00      B1
ATOM  1802 CZ2 TRP 259     24.531  33.486  19.195  1.00 47.40      B1
ATOM  1803 CZ3 TRP 259     24.317  31.344  18.097  1.00 49.07      B1
ATOM  1804 CH2 TRP 259     24.613  32.706  18.050  1.00 49.12      B1
ATOM  1805 C  TRP 259     25.459  29.727  23.440  1.00 44.01      B1
ATOM  1806 O  TRP 259     25.340  29.664  24.671  1.00 43.25      B1
ATOM  1807 N  ALA 260     26.469  30.247  22.777  1.00 43.01      B1
ATOM  1808 H  ALA 260     26.523  30.198  21.796  1.00  0.00      B1
ATOM  1809 CA ALA 260     27.493  30.973  23.482  1.00 43.48      B1
ATOM  1810 CB ALA 260     28.874  30.549  22.969  1.00 43.33      B1
ATOM  1811 C  ALA 260     27.249  32.486  23.216  1.00 43.41      B1
ATOM  1812 O  ALA 260     27.315  32.946  22.054  1.00 40.55      B1
ATOM  1813 N  PRO 261     26.853  33.267  24.253  1.00 42.43      B1
ATOM  1814 CD PRO 261     26.527  32.807  25.606  1.00 42.33      B1
ATOM  1815 CA PRO 261     26.720  34.701  24.199  1.00 42.37      B1
ATOM  1816 CB PRO 261     25.778  34.987  25.335  1.00 41.46      B1
ATOM  1817 CG PRO 261     26.251  34.060  26.411  1.00 42.00      B1
ATOM  1818 C  PRO 261     28.087  35.369  24.311  1.00 42.22      B1
ATOM  1819 O  PRO 261     28.988  34.956  25.037  1.00 38.82      B1
ATOM  1820 N  LEU 262     28.234  36.403  23.486  1.00 45.20      B1
ATOM  1821 H  LEU 262     27.513  36.610  22.853  1.00  0.00      B1
ATOM  1822 CA LEU 262     29.434  37.210  23.498  1.00 46.50      B1
ATOM  1823 CB LEU 262     30.531  36.609  22.610  1.00 45.09      B1
ATOM  1824 CG LEU 262     31.903  37.157  22.964  1.00 42.55      B1
ATOM  1825 CD1 LEU 262     32.344  36.695  24.338  1.00 41.52      B1
ATOM  1826 CD2 LEU 262     32.850  36.730  21.900  1.00 44.21      B1
ATOM  1827 C  LEU 262     29.154  38.628  23.035  1.00 48.56      B1
ATOM  1828 O  LEU 262     29.633  39.470  23.790  1.00 48.73      B1
ATOM  1829 N  SER 263     28.388  38.956  21.960  1.00 51.33      B1
ATOM  1830 H  SER 263     27.982  38.242  21.427  1.00  0.00      B1
ATOM  1831 CA SER 263     28.127  40.339  21.494  1.00 55.19      B1
ATOM  1832 CB SER 263     26.871  40.511  20.612  1.00 57.17      B1
ATOM  1833 OG SER 263     26.498  39.411  19.776  1.00 64.32      B1
ATOM  1834 HG SER 263     26.093  38.741  20.336  1.00  0.00      B1
```

FIGURE 5

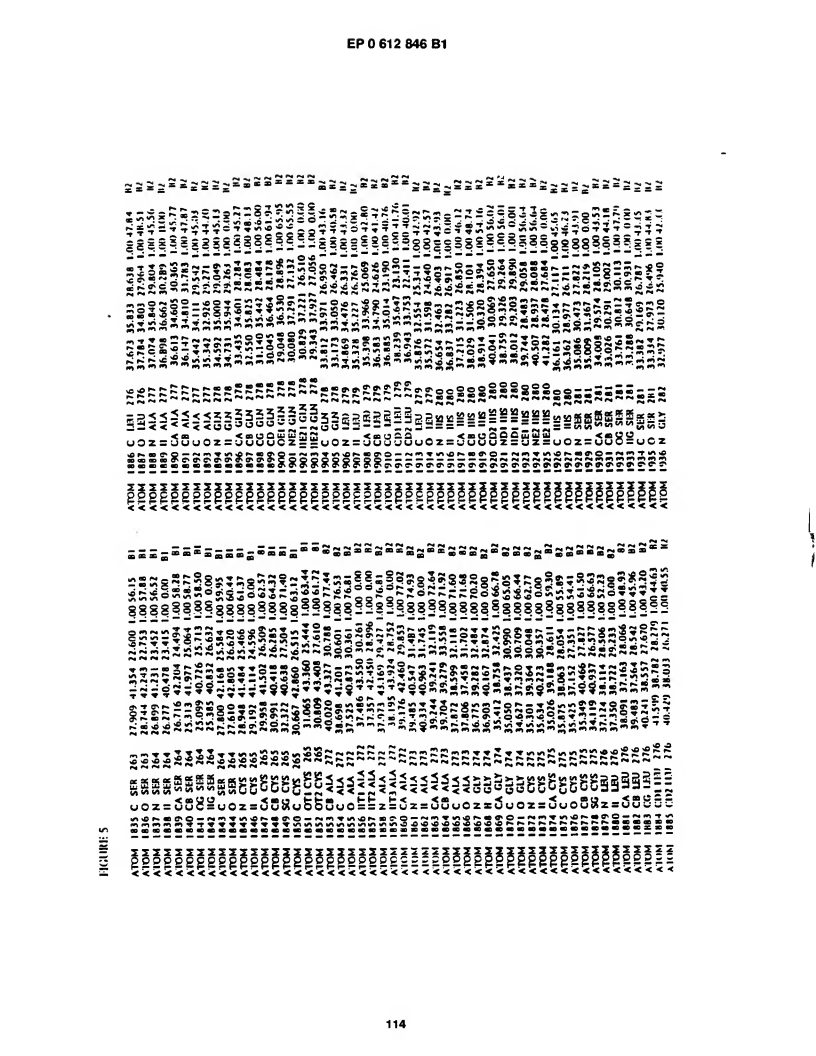


FIGURE 5

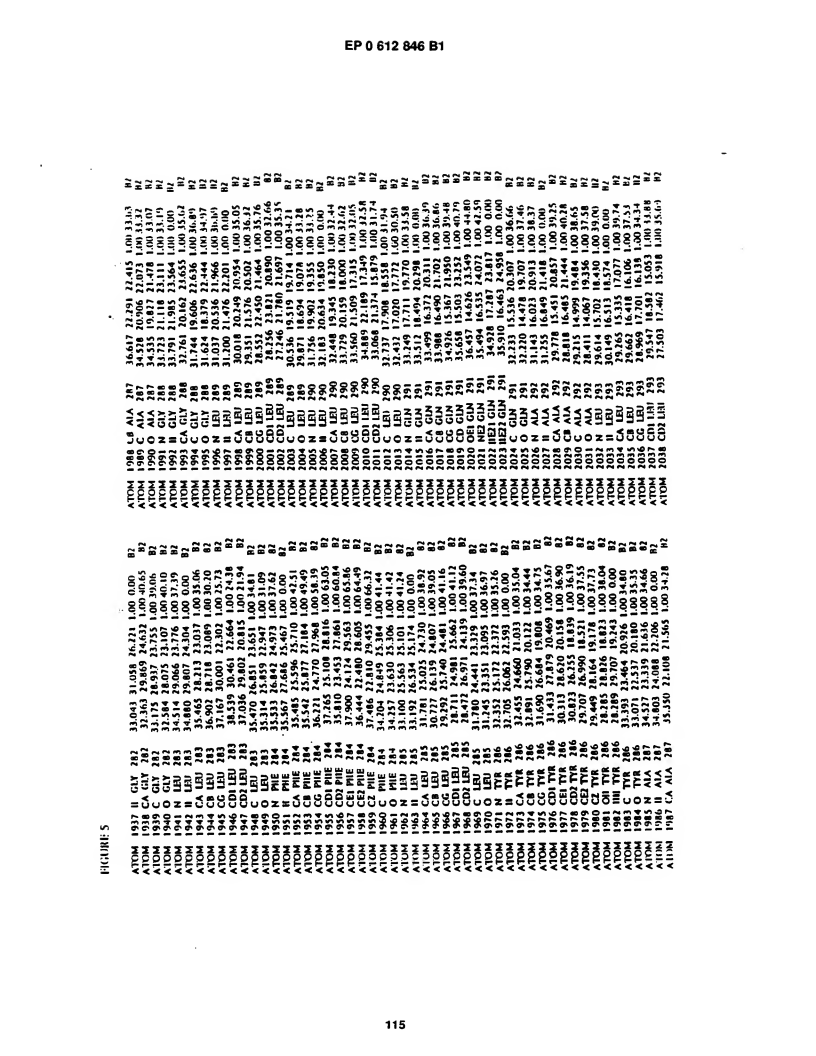


FIGURE 5

```
ATOM  2039 C  LEU  293      29.933  14.060  16.596  1.00 40.86      B2
ATOM  2040 O  LEU  293      29.686  13.669  15.449  1.00 40.58      B2
ATOM  2041 N  GLU  294      30.887  13.495  17.365  1.00 42.12      B2
ATOM  2042 H  GLU  294      31.131  13.963  18.190  1.00  0.00      B2
ATOM  2043 CA GLU  294      31.598  12.253  17.076  1.00 42.89      B2
ATOM  2044 CB GLU  294      30.806  10.984  17.485  1.00 48.38      B2
ATOM  2045 CG GLU  294      30.715  10.614  18.972  1.00 56.26      B2
ATOM  2046 CD GLU  294      29.271  10.408  19.486  1.00 63.70      B2
ATOM  2047 OE1 GLU  294     29.058  10.603  20.702  1.00 67.72      B2
ATOM  2048 OE2 GLU  294     28.363  10.074  18.692  1.00 64.81      B2
ATOM  2049 C  GLU  294      31.972  12.068  15.632  1.00 41.53      B2
ATOM  2050 O  GLU  294      31.804  11.007  15.021  1.00 40.29      B2
ATOM  2051 N  GLY  295      32.424  13.103  15.106  1.00 40.93      B2
ATOM  2052 H  GLY  295      32.357  14.033  15.621  1.00  0.00      B2
ATOM  2053 CA GLY  295      32.998  13.236  13.783  1.00 39.95      B2
ATOM  2054 C  GLY  295      32.027  13.230  12.634  1.00 40.60      B2
ATOM  2055 O  GLY  295      32.477  13.216  11.487  1.00 40.96      B2
ATOM  2056 N  ILE  296      30.728  13.296  12.898  1.00 41.18      B2
ATOM  2057 H  ILE  296      30.446  13.210  13.825  1.00  0.00      B2
ATOM  2058 CA ILE  296      29.687  13.306  11.888  1.00 44.02      B2
ATOM  2059 CB ILE  296      29.683  14.580  11.009  1.00 43.49      B2
ATOM  2060 CG2 ILE  296     28.288  14.685  10.421  1.00 40.56      B2
ATOM  2061 CG1 ILE  296     30.047  15.831  11.793  1.00 45.11      B2
ATOM  2062 CD ILE  296      30.039  17.189  11.062  1.00 46.06      B2
ATOM  2063 C  ILE  296      29.820  12.107  10.949  1.00 46.71      B2
ATOM  2064 O  ILE  296      28.918  11.279  11.060  1.00 50.61      B2
ATOM  2065 N  SER  297      30.767  11.875  10.019  1.00 47.21      B2
ATOM  2066 H  SER  297      31.526  12.491  9.936  1.00  0.00      B2
ATOM  2067 CA SER  297      30.810  10.646  9.234  1.00 46.73      B2
ATOM  2068 CB SER  297      30.239  10.884  7.865  1.00 45.48      B2
ATOM  2069 OG SER  297      30.988  11.782  7.072  1.00 46.27      B2
ATOM  2070 HG SER  297      30.321  12.200  6.503  1.00  0.00      B2
ATOM  2071 C  SER  297      32.263  10.269  9.123  1.00 46.50      B2
ATOM  2072 O  SER  297      33.120  11.122  9.391  1.00 50.55      B2
ATOM  2073 N  PRO  298      32.655  9.069  8.697  1.00 49.68      B2
ATOM  2074 CD PRO  298      31.782  7.964  8.334  1.00 50.62      B2
ATOM  2075 CA PRO  298      34.049  8.701  8.458  1.00 50.33      B2
ATOM  2076 CB PRO  298      33.948  7.308  7.856  1.00 51.53      B2
ATOM  2077 CG PRO  298      32.576  7.266  7.231  1.00 50.43      B2
ATOM  2078 C  PRO  298      34.795  9.692  7.579  1.00 50.08      B2
ATOM  2079 O  PRO  298      35.883  10.137  7.930  1.00 50.50      B2
ATOM  2080 N  GLN  299      34.173  10.086  6.469  1.00 50.48      B2
ATOM  2081 H  GLN  299      33.279  9.729  6.296  1.00  0.00      B2
ATOM  2082 CA GLN  299      34.749  11.050  5.550  1.00 51.74      B2
ATOM  2083 CB GLN  299      33.898  11.236  4.301  1.00 54.33      B2
ATOM  2084 CG GLN  299      33.095  10.067  3.725  1.00 58.11      B2
ATOM  2085 CD GLN  299      31.658  10.086  4.259  1.00 61.49      B2
ATOM  2086 OE1 GLN  299     31.160  9.083  4.776  1.00 61.00      B2
ATOM  2087 NE2 GLN  299     30.942  11.217  4.204  1.00 62.12      B2
ATOM  2088 HE21 GLN  299    31.345  12.012  3.800  1.00  0.00      B2
ATOM  2089 HE22 GLN  299    30.034  11.191  4.566  1.00  0.00      B2

ATOM  2090 C  GLN  299      34.923  12.453  6.160  1.00 51.04      B2
ATOM  2091 O  GLN  299      35.796  13.186  5.718  1.00 53.38      B2
ATOM  2092 N  LEU  300      34.118  12.918  7.120  1.00 48.15      B2
ATOM  2093 H  LEU  300      33.382  12.351  7.437  1.00  0.00      B2
ATOM  2094 CA LEU  300      34.272  14.220  7.745  1.00 45.32      B2
ATOM  2095 CB LEU  300      32.856  14.719  8.021  1.00 41.39      B2
ATOM  2096 CG LEU  300      32.073  15.546  6.974  1.00 37.99      B2
ATOM  2097 CD1 LEU  300     31.872  14.824  5.648  1.00 38.54      B2
ATOM  2098 CD2 LEU  309     30.705  15.809  7.527  1.00 37.67      B2
ATOM  2099 C  LEU  300      35.142  14.220  9.019  1.00 42.84      B2
ATOM  2100 O  LEU  300      35.558  15.278  9.541  1.00 37.60      B2
ATOM  2101 N  GLY  301      35.467  13.016  9.528  1.00 40.83      B2
ATOM  2102 H  GLY  301      35.157  12.221  9.046  1.00  0.00      B2
ATOM  2103 CA GLY  301      36.199  12.826  10.779  1.00 36.72      B2
ATOM  2104 C  GLY  301      37.500  13.607  10.887  1.00 37.99      B2
ATOM  2105 O  GLY  301      37.665  14.406  11.809  1.00 37.31      B2
ATOM  2106 N  PRO  302      38.468  13.452  9.985  1.00 37.33      B2
ATOM  2107 CD PRO  302      38.353  12.630  8.790  1.00 37.77      B2
ATOM  2108 CA PRO  302      39.676  14.281  9.864  1.00 37.60      B2
ATOM  2109 CB PRO  302      40.256  13.907  8.541  1.00 36.62      B2
ATOM  2110 CG PRO  302      39.047  13.487  7.745  1.00 37.94      B2
ATOM  2111 C  PRO  302      39.486  15.782  10.033  1.00 37.45      B2
ATOM  2112 O  PRO  302      40.132  16.398  10.901  1.00 38.31      B2
ATOM  2113 N  THR  303      38.547  16.311  9.204  1.00 37.05      B2
ATOM  2114 H  THR  303      38.085  15.727  8.567  1.00  0.00      B2
ATOM  2115 CA THR  303      38.119  17.705  9.128  1.00 35.81      B2
ATOM  2116 CB THR  303      36.963  17.770  8.123  1.00 37.26      B2
ATOM  2117 OG1 THR  303     37.416  17.161  6.909  1.00 39.64      B2
ATOM  2118 HG1 THR  303     37.369  17.785  6.178  1.00  0.00      B2
ATOM  2119 CG2 THR  303     36.469  19.204  7.927  1.00 38.55      B2
ATOM  2120 C  THR  303      37.687  18.223  10.505  1.00 34.93      B2
ATOM  2121 O  THR  303      38.085  19.263  11.063  1.00 35.31      B2
ATOM  2122 N  LEU  304      36.928  17.366  11.159  1.00 33.76      B2
ATOM  2123 H  LEU  304      36.672  16.500  10.762  1.00  0.00      B2
ATOM  2124 CA LEU  304      36.436  17.746  12.418  1.00 31.01      B2
ATOM  2125 CB LEU  304      35.345  16.803  12.708  1.00 30.31      B2
ATOM  2126 CG LEU  304      34.234  17.567  13.320  1.00 31.32      B2
ATOM  2127 CD1 LEU  304     33.121  17.676  12.309  1.00 28.87      B2
ATOM  2128 CD2 LEU  304     33.921  16.970  14.692  1.00 34.23      B2
ATOM  2129 C  LEU  304      37.553  17.726  13.421  1.00 31.86      B2
ATOM  2130 O  LEU  304      37.615  18.623  14.259  1.00 34.21      B2
ATOM  2131 N  ASP  305      38.510  16.811  13.326  1.00 30.56      B2
ATOM  2132 H  ASP  305      38.456  16.117  12.635  1.00  0.00      B2
ATOM  2133 CA ASP  305      39.576  16.797  14.303  1.00 30.72      B2
ATOM  2134 CB ASP  305      40.504  15.608  14.114  1.00 36.20      B2
ATOM  2135 CG ASP  305      39.912  14.201  14.288  1.00 40.64      B2
ATOM  2136 OD1 ASP  305     38.976  14.040  15.103  1.00 37.52      B2
ATOM  2137 OD2 ASP  305     40.426  13.304  13.581  1.00 42.19      B2
ATOM  2138 C  ASP  305      40.435  18.054  14.238  1.00 27.56      B2
ATOM  2139 O  ASP  305      40.775  18.575  15.311  1.00 24.61      B2
ATOM  2140 N  THR  306      40.781  18.417  12.979  1.00 24.77      B2
```

FIGURE 5

```
ATOM  2141  H  THR  306      40.469  17.875  12.230  1.00  0.00      B2
ATOM  2142  CA THR  306      41.553  19.633  12.751  1.00 24.39      B2
ATOM  2143  CB THR  306      41.665  19.931  11.318  1.00 24.58      B2
ATOM  2144  OG1 THR  306     42.074  18.753  10.665  1.00 25.13      B2
ATOM  2145  1IG1 THR  306    41.447  18.029  10.768  1.00  0.00      B2
ATOM  2146  CG2 THR  306     42.690  21.027  11.089  1.00 25.77      B2
ATOM  2147  C  THR  306      40.893  20.844  13.419  1.00 25.24      B2
ATOM  2148  O  THR  306      41.488  21.472  14.296  1.00 27.24      B2
ATOM  2149  N  LEU  307      39.615  21.134  13.139  1.00 25.91      B2
ATOM  2150  H  LEU  307      39.125  20.547  12.520  1.00  0.00      B2
ATOM  2151  CA LEU  307     38.900  22.228  13.764  1.00 25.53      B2
ATOM  2152  CB LEU  307     37.571  22.170  13.142  1.00 25.09      B2
ATOM  2153  CG LEU  307     36.530  23.097  13.588  1.00 27.93      B2
ATOM  2154  CD1 LEU  307    37.008  24.515  13.484  1.00 29.87      B2
ATOM  2155  CD2 LEU  307    35.311  22.846  12.728  1.00 28.93      B2
ATOM  2156  C  LEU  307      38.850  22.214  15.269  1.00 27.09      B2
ATOM  2157  O  LEU  307      38.854  23.253  15.925  1.00 30.03      B2
ATOM  2158  N  GLN  308      38.875  21.044  15.879  1.00 29.09      B2
ATOM  2159  H  GLN  308      38.883  20.239  15.319  1.00  0.00      B2
ATOM  2160  CA GLN  308     38.824  20.848  17.340  1.00 29.36      B2
ATOM  2161  CB GLN  308     38.379  19.399  17.562  1.00 29.41      B2
ATOM  2162  CG GLN  309     37.862  19.140  18.935  1.00 32.24      B2
ATOM  2163  CD GLN  309     37.586  17.672  19.165  1.00 34.03      B2
ATOM  2164  OE1 GLN  308    36.973  17.023  18.311  1.00 33.48      B2
ATOM  2165  NE2 GLN  308    38.053  17.127  20.299  1.00 31.67      B2
ATOM  2166  1IE2 GLN  308   38.547  17.697  20.917  1.00  0.00      B2
ATOM  2167  1IE2 GLN  308   37.875  16.174  20.436  1.00  0.00      B2
ATOM  2168  C  GLN  308      40.154  21.138  18.051  1.00 28.94      B2
ATOM  2169  O  GLN  308      40.196  21.796  19.101  1.00 28.44      B2
ATOM  2170  N  LEU  309      41.269  20.671  17.460  1.00 28.78      B2
ATOM  2171  H  LEU  309      41.157  20.120  16.655  1.00  0.00      B2
ATOM  2172  CA LEU  309     42.632  20.923  17.967  1.00 28.56      B2
ATOM  2173  CB LEU  309     43.671  20.154  17.106  1.00 26.54      B2
ATOM  2174  CG LEU  309     43.632  18.636  17.241  1.00 24.98      B2
ATOM  2175  CD1 LEU  309    44.595  17.935  16.353  1.00 24.17      B2
ATOM  2176  CD2 LEU  309    43.992  18.310  18.621  1.00 23.45      B2
ATOM  2177  C  LEU  309      42.893  22.416  17.909  1.00 28.24      B2
ATOM  2178  O  LEU  309      43.370  22.957  18.907  1.00 30.32      B2
ATOM  2179  N  ASP  310      42.548  23.027  16.749  1.00 26.58      B2
ATOM  2180  H  ASP  310      42.296  22.437  16.007  1.00  0.00      B2
ATOM  2181  CA ASP  310     42.495  24.477  16.495  1.00 27.90      B2
ATOM  2182  CB ASP  310     42.025  24.659  15.076  1.00 28.41      B2
ATOM  2183  CG ASP  310     43.162  24.556  14.096  1.00 31.84      B2
ATOM  2184  OD1 ASP  310    42.959  24.766  12.905  1.00 31.54      B2
ATOM  2185  OD2 ASP  310    44.297  24.314  14.514  1.00 37.32      B2
ATOM  2186  C  ASP  310      41.666  25.410  17.422  1.00 27.99      B2
ATOM  2187  O  ASP  310      42.219  26.429  17.876  1.00 27.23      B2
ATOM  2188  N  VAL  311      40.374  25.086  17.725  1.00 26.29      B2
ATOM  2189  H  VAL  311      39.961  24.347  17.225  1.00  0.00      B2
ATOM  2190  CA VAL  311     39.546  25.803  18.706  1.00 24.29      B2
ATOM  2191  CB VAL  311     38.098  25.217  18.869  1.00 21.47      B2
ATOM  2192  CG1 VAL  311    37.341  25.915  19.949  1.00 19.01      B2
ATOM  2193  CG2 VAL  311    37.261  25.488  17.667  1.00 18.56      B2
ATOM  2194  C  VAL  311     40.270  25.638  20.020  1.00 27.21      B2
ATOM  2195  O  VAL  311     40.437  26.647  20.719  1.00 29.71      B2
ATOM  2196  N  AIA  312     40.762  24.428  20.357  1.00 27.97      B2
ATOM  2197  H  AIA  312     40.585  23.674  19.756  1.00  0.00      B2
ATOM  2198  CA ALA  312     41.515  24.157  21.583  1.00 29.23      B2
ATOM  2199  CB AIA  312     41.855  22.688  21.552  1.00 30.53      B2
ATOM  2200  C  AIA  312     42.778  25.026  21.784  1.00 30.06      B2
ATOM  2201  O  AIA  312     43.057  25.508  22.886  1.00 30.04      B2
ATOM  2202  N  ASP  313     43.554  25.286  20.735  1.00 31.43      B2
ATOM  2203  H  ASP  313     43.431  24.730  19.935  1.00  0.00      B2
ATOM  2204  CA ASP  313     44.610  26.275  20.743  1.00 34.22      B2
ATOM  2205  CB ASP  313     45.279  26.512  19.447  1.00 38.87      B2
ATOM  2206  CG ASP  313     46.071  25.404  18.866  1.00 44.55      B2
ATOM  2207  OD1 ASP  313    46.225  25.439  17.636  1.00 48.67      B2
ATOM  2208  OD2 ASP  313    46.521  24.553  19.647  1.00 49.25      B2
ATOM  2209  C  ASP  313      44.187  27.699  21.059  1.00 35.12      B2
ATOM  2210  O  ASP  313      44.807  28.390  21.894  1.00 38.60      B2
ATOM  2211  N  PHE  314      43.192  28.216  20.319  1.00 33.36      B2
ATOM  2212  H  PHE  314      42.784  27.683  19.619  1.00  0.00      B2
ATOM  2213  CA PHE  314     42.715  29.548  20.600  1.00 31.09      B2
ATOM  2214  CB PHE  314     41.572  29.860  19.633  1.00 32.06      B2
ATOM  2215  CG PHE  314     41.074  31.303  19.636  1.00 33.17      B2
ATOM  2216  CD1 PHE  314    39.780  31.568  19.247  1.00 31.81      B2
ATOM  2217  CD2 PHE  314    41.907  32.354  20.021  1.00 35.05      B2
ATOM  2218  CE1 PHE  314    39.318  32.857  19.240  1.00 29.15      B2
ATOM  2219  CE2 PHE  314    41.455  33.648  20.017  1.00 33.48      B2
ATOM  2220  CZ PHE  314     40.154  33.870  19.622  1.00 32.81      B2
ATOM  2221  C  PHE  314     42.282  29.601  22.057  1.00 29.90      B2
ATOM  2222  O  PHE  314     42.658  30.550  22.764  1.00 26.87      B2
ATOM  2223  N  AIA  315     41.686  28.532  22.594  1.00 29.29      B2
ATOM  2224  H  AIA  315     41.448  27.764  22.022  1.00  0.00      B2
ATOM  2225  CA ALA  315     41.300  28.583  23.961  1.00 31.61      B2
ATOM  2226  CB ALA  315     40.632  27.358  24.451  1.00 32.23      B2
ATOM  2227  C  ALA  315     42.482  28.751  24.836  1.00 34.41      B2
ATOM  2228  O  AIA  315     42.361  29.437  25.853  1.00 37.66      B2
ATOM  2229  N  THR  316     43.646  28.250  24.476  1.00 36.16      B2
ATOM  2230  H  THR  316     43.745  27.778  23.625  1.00  0.00      B2
ATOM  2231  CA THR  316     44.780  28.388  25.374  1.00 37.99      B2
ATOM  2232  CB THR  316     45.795  27.255  25.156  1.00 41.16      B2
ATOM  2233  OG1 THR  316    45.049  26.081  25.521  1.00 45.50      B2
ATOM  2234  1IG1 THR  316    44.316  25.900  24.911  1.00  0.00      B2
ATOM  2235  CG2 THR  316    47.152  27.415  25.888  1.00 40.31      B2
ATOM  2236  C  THR  316      45.458  29.710  25.177  1.00 38.47      B2
ATOM  2237  O  THR  316      45.903  30.189  26.217  1.00 39.63      B2
ATOM  2238  N  THR  317      45.620  30.287  23.970  1.00 36.53      B2
ATOM  2239  H  THR  317      45.351  29.800  23.164  1.00 31.00      B2
ATOM  2240  CA THR  317     46.092  31.657  23.844  1.00 37.07      B2
ATOM  2241  CB THR  317     45.866  32.098  22.392  1.00 36.01      B2
ATOM  2242  OG1 THR  317     46.752  31.352  21.575  1.00 35.41      B2
```

FIGURE 5

```
ATOM  2243 HG1 THR  317      46.489  30.441  21.389  1.00  0.00      B2
ATOM  2244 CG2 THR  317      46.109  33.566  22.156  1.00 34.30      B2
ATOM  2245 C   THR  317      45.338  32.597  24.832  1.00 39.30      B2
ATOM  2246 O   THR  317      45.941  33.378  25.583  1.00 40.17      B2
ATOM  2247 N   ILE  318      44.003  32.481  24.912  1.00 40.83      B2
ATOM  2248 H   ILE  318      43.554  31.819  24.342  1.00  0.00      B2
ATOM  2249 CA  ILE  318      43.172  33.317  25.788  1.00 40.75      B2
ATOM  2250 CB  ILE  318      41.621  32.979  25.567  1.00 37.17      B2
ATOM  2251 CG2 ILE  318      40.742  33.706  26.545  1.00 34.29      B2
ATOM  2252 CG1 ILE  318      41.216  33.310  24.160  1.00 31.39      B2
ATOM  2253 CD  ILE  318      41.626  34.657  23.614  1.00 29.66      B2
ATOM  2254 C   ILE  318      43.624  33.019  27.217  1.00 42.43      B2
ATOM  2255 O   ILE  318      44.064  33.963  27.856  1.00 42.54      B2
ATOM  2256 N   TRP  319      43.662  31.784  27.744  1.00 44.17      B2
ATOM  2257 H   TRP  319      43.537  31.008  27.163  1.00  0.00      B2
ATOM  2258 CA  TRP  319      43.994  31.633  29.142  1.00 46.90      B2
ATOM  2259 CB  TRP  319      43.892  30.179  29.597  1.00 50.64      B2
ATOM  2260 CG  TRP  319      43.998  30.094  31.131  1.00 56.05      B2
ATOM  2261 CD2 TRP  319      43.005  30.397  32.038  1.00 58.61      B2
ATOM  2262 CE2 TRP  319      43.685  30.281  33.251  1.00 60.50      B2
ATOM  2263 CE3 TRP  319      41.668  30.740  32.005  1.00 60.12      B2
ATOM  2264 CD1 TRP  319      45.188  29.788  31.760  1.00 58.07      B2
ATOM  2265 NE1 TRP  319      44.968  29.921  33.042  1.00 60.07      B2
ATOM  2266 HE1 TRP  319      45.637  29.765  33.740  1.00  0.00      B2
ATOM  2267 CZ2 TRP  319      43.044  30.512  34.456  1.00 61.00      B2
ATOM  2268 CZ3 TRP  319      41.022  30.967  33.210  1.00 61.58      B2
ATOM  2269 CH2 TRP  319      41.704  30.854  34.417  1.00 62.04      B2
ATOM  2270 C   TRP  319      45.398  32.136  29.456  1.00 47.85      B2
ATOM  2271 O   TRP  319      45.635  32.772  30.490  1.00 47.98      B2
ATOM  2272 N   GLN  320      46.339  31.915  28.550  1.00 48.63      B2
ATOM  2273 H   GLN  320      46.091  31.482  27.708  1.00  0.00      B2
ATOM  2274 CA  GLN  320      47.706  32.319  28.767  1.00 49.45      B2
ATOM  2275 CB  GLN  320      48.567  31.988  27.589  1.00 51.44      B2
ATOM  2276 CG  GLN  320      48.828  30.494  27.444  1.00 55.03      B2
ATOM  2277 CD  GLN  320      49.958  30.349  26.438  1.00 60.17      B2
ATOM  2278 OE1 GLN  320      51.116  30.465  26.834  1.00 65.26      B2
ATOM  2279 NE2 GLN  320      49.771  30.145  25.133  1.00 59.32      B2
ATOM  2280 HE21 GLN  320      48.859  30.087  24.789  1.00  0.00      B2
ATOM  2281 HE22 GLN  320      50.582  30.083  24.590  1.00  0.00      B2
ATOM  2282 C   GLN  320      47.717  33.790  28.983  1.00 49.62      B2
ATOM  2283 O   GLN  320      48.251  34.209  29.987  1.00 49.91      B2
ATOM  2284 N   GLN  321      46.998  34.538  28.150  1.00 51.76      B2
ATOM  2285 H   GLN  321      46.535  34.102  27.403  1.00  0.00      B2
ATOM  2286 CA  GLN  321      46.837  35.988  28.278  1.00 52.08      B2
ATOM  2287 CB  GLN  321      45.873  38.058  27.166  1.00 51.19      B2
ATOM  2288 CG  GLN  321      47.211  38.781  27.201  1.00 53.13      B2
ATOM  2289 CD  GLN  321      48.090  38.622  26.364  1.00 55.36      B2
ATOM  2290 OE1 GLN  321      47.468  39.618  28.177  1.00 53.21      B2
ATOM  2291 NE2 GLN  321      46.800  39.713  28.889  1.00  0.00      B2
ATOM  2292 HE21 GLN  321      48.338  40.057  28.168  1.00  0.00      B2
ATOM  2293 HE22 GLN  321

ATOM  2294 C   GLN  321      46.112  36.315  29.562  1.00 53.30      B2
ATOM  2295 O   GLN  321      46.293  37.422  30.058  1.00 54.39      B2
ATOM  2296 N   MET  322      45.269  35.441  30.117  1.00 54.50      B2
ATOM  2297 H   MET  322      45.098  34.592  29.662  1.00  0.00      B2
ATOM  2298 CA  MET  322      44.619  35.748  31.375  1.00 55.42      B2
ATOM  2299 CB  MET  322      43.595  34.690  31.713  1.00 52.98      B2
ATOM  2300 CG  MET  322      42.527  34.865  30.658  1.00 51.76      B2
ATOM  2301 SD  MET  322      40.861  34.428  31.189  1.00 54.19      B2
ATOM  2302 CE  MET  322      40.293  33.192  30.069  1.00 52.53      B2
ATOM  2303 C   MET  322      45.700  35.811  32.432  1.00 57.69      B2
ATOM  2304 O   MET  322      45.781  36.739  33.248  1.00 57.65      B2
ATOM  2305 N   GLU  323      46.657  34.900  32.319  1.00 60.28      B2
ATOM  2306 H   GLU  323      46.637  34.296  31.544  1.00  0.00      B2
ATOM  2307 CA  GLU  323      47.741  34.875  33.273  1.00 62.99      B2
ATOM  2308 CB  GLU  323      48.558  33.635  32.957  1.00 65.81      B2
ATOM  2309 CG  GLU  323      47.640  32.423  32.918  1.00 68.36      B2
ATOM  2310 CD  GLU  323      48.303  31.125  33.310  1.00 71.21      B2
ATOM  2311 OE1 GLU  323      47.651  30.364  34.044  1.00 71.19      B2
ATOM  2312 OE2 GLU  323      49.451  30.900  32.884  1.00 72.43      B2
ATOM  2313 C   GLU  323      48.648  36.124  33.418  1.00 63.96      B2
ATOM  2314 OT1 GLU  323      48.782  36.492  34.584  1.00 64.11      B2
ATOM  2315 OT2 GLU  323      49.169  36.725  32.449  1.00 62.96      B2
ATOM  2316 CB  MET  338      27.559  17.690  25.056  1.00 62.56      B3
ATOM  2317 CG  MET  338      28.087  18.862  24.222  1.00 63.85      B3
ATOM  2318 SD  MET  338      28.738  20.224  25.219  1.00 66.95      B3
ATOM  2319 CE  MET  338      27.328  21.252  25.515  1.00 65.50      B3
ATOM  2320 C   MET  338      24.598  17.301  25.122  1.00 57.55      B3
ATOM  2321 O   MET  338      24.417  16.347  25.667  1.00 56.47      B3
ATOM  2322 HT1 MET  338      26.255  16.010  26.594  1.00  0.00      B3
ATOM  2323 HT2 MET  338      25.375  17.061  27.500  1.00  0.00      B3
ATOM  2324 N   MET  338      26.286  16.971  27.009  1.00 61.55      B3
ATOM  2325 HT3 MET  338      27.108  17.107  27.620  1.00  0.00      B3
ATOM  2326 CA  MET  338      26.226  17.853  25.851  1.00 60.35      B3
ATOM  2327 N   PRO  339      24.493  17.830  23.998  1.00 55.58      B3
ATOM  2328 CD  PRO  339      24.914  19.075  23.375  1.00 54.39      B3
ATOM  2329 CA  PRO  339      23.453  17.226  23.164  1.00 54.62      B3
ATOM  2330 CB  PRO  339      23.463  18.098  21.903  1.00 53.52      B3
ATOM  2331 CG  PRO  339      24.845  18.711  21.909  1.00 53.04      B3
ATOM  2332 C   PRO  339      23.666  15.748  22.881  1.00 53.61      B3
ATOM  2333 O   PRO  339      24.730  15.222  23.169  1.00 53.55      B3
ATOM  2334 N   ALA  340      22.704  15.045  22.333  1.00 54.32      B3
ATOM  2335 H   ALA  340      21.844  15.460  22.111  1.00  0.00      B3
ATOM  2336 CA  ALA  340      22.909  13.651  23.968  1.00 56.04      B3
ATOM  2337 CB  ALA  340      21.867  12.713  22.625  1.00 57.60      B3
ATOM  2338 C   ALA  340      22.617  13.713  20.495  1.00 55.61      B3
ATOM  2339 O   ALA  340      21.426  13.783  20.196  1.00 58.64      B3
ATOM  2340 N   PHE  341      23.516  13.734  19.514  1.00 53.34      B3
ATOM  2341 H   PHE  341      24.472  13.607  19.685  1.00  0.00      B3
ATOM  2342 CA  PHE  341      23.016  13.900  18.158  1.00 49.92      B3
ATOM  2343 CB  PHE  341      24.050  14.541  17.244  1.00 48.16      B3
ATOM  2344 CG  PHE  341      24.382  15.940  17.658  1.00 45.00      B3
```

FIGURE 5

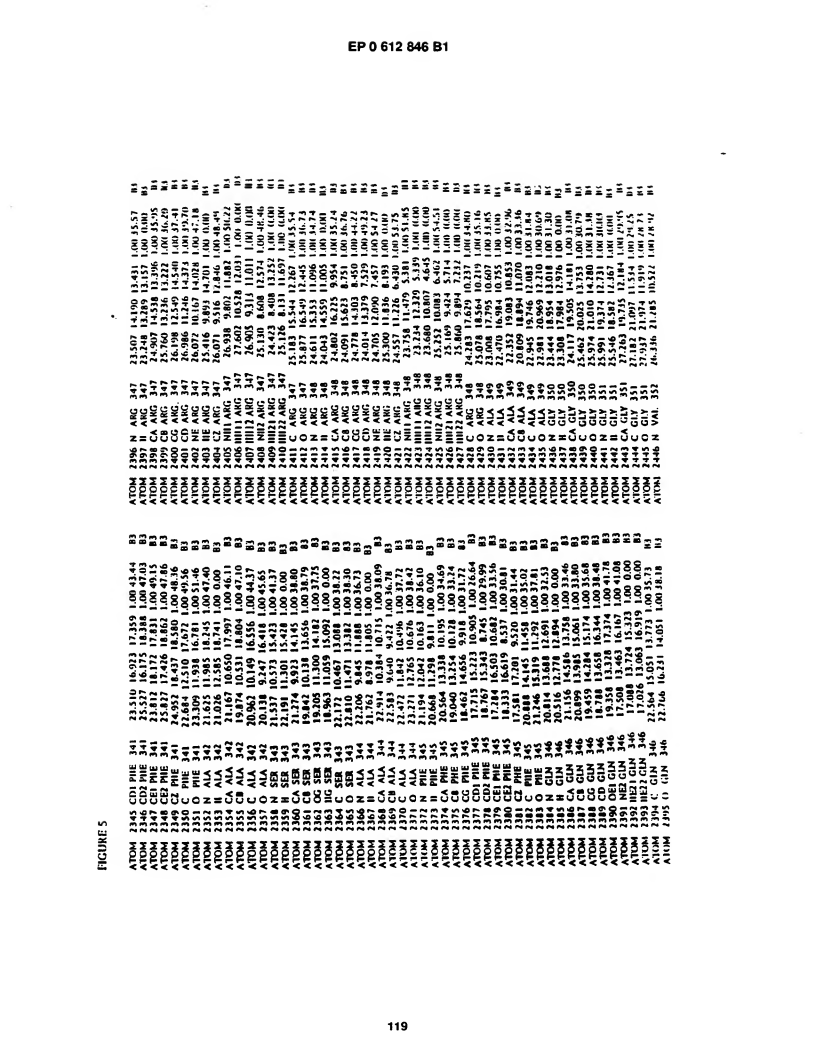


FIGURE 5

```
ATOM  2447 H  VAL  352      25.859  20.484  10.214  1.00  0.00      B3
ATOM  2448 CA VAL  352      26.079  22.567   9.881  1.00 28.59      B3
ATOM  2449 CB VAL  352      24.845  22.452   9.004  1.00 28.96      B3
ATOM  2450 CG1 VAL  352     24.627  23.785   8.346  1.00 30.86      B3
ATOM  2451 CG2 VAL  352     25.021  21.475   7.875  1.00 26.94      B3
ATOM  2452 C  VAL  352      25.849  23.709  10.890  1.00 29.29      B3
ATOM  2453 O  VAL  352      26.520  24.747  10.853  1.00 31.02      B3
ATOM  2454 N  LEU  353      24.923  23.543  11.819  1.00 27.52      B3
ATOM  2455 H  LEU  353      24.404  22.709  11.838  1.00  0.00      B3
ATOM  2456 CA LEU  353      24.635  24.548  12.817  1.00 26.18      B3
ATOM  2457 CB LEU  353      23.434  24.113  13.636  1.00 27.87      B3
ATOM  2458 CG LEU  353      22.098  24.034  12.931  1.00 26.54      B3
ATOM  2459 CD1 LEU  353     21.064  23.617  13.924  1.00 25.49      B3
ATOM  2460 CD2 LEU  353     21.750  25.372  12.320  1.00 28.23      B3
ATOM  2461 C  LEU  353      25.742  24.905  13.772  1.00 27.17      B3
ATOM  2462 O  LEU  353      25.838  26.093  14.088  1.00 28.00      B3
ATOM  2463 N  VAL  354      26.539  23.949  14.318  1.00 27.20      B3
ATOM  2464 H  VAL  354      26.321  23.006  14.139  1.00  0.00      B3
ATOM  2465 CA VAL  354      27.712  24.212  15.157  1.00 24.62      B3
ATOM  2466 CB VAL  354      28.736  22.910  15.745  1.00 22.01      B3
ATOM  2467 CG1 VAL  354     29.568  23.089  16.406  1.00 19.82      B3
ATOM  2468 CG2 VAL  354     27.276  22.467  16.802  1.00 23.96      B3
ATOM  2469 C  VAL  354      28.812  24.893  14.332  1.00 25.46      B3
ATOM  2470 O  VAL  354      29.439  25.832  14.798  1.00 26.23      B3
ATOM  2471 N  ALA  355      29.059  24.530  13.089  1.00 26.12      B3
ATOM  2472 H  ALA  355      28.579  23.705  12.711  1.00  0.00      B3
ATOM  2473 CA ALA  355      30.025  25.180  12.235  1.00 26.54      B3
ATOM  2474 CB ALA  355      30.034  24.591  10.869  1.00 22.08      B3
ATOM  2475 C  ALA  355      29.533  26.601  12.096  1.00 28.51      B3
ATOM  2476 O  ALA  355      30.315  27.498  12.344  1.00 31.93      B3
ATOM  2477 N  SER  356      28.271  26.884  11.802  1.00 30.30      B3
ATOM  2478 H  SER  356      27.654  26.134  11.665  1.00  0.00      B3
ATOM  2479 CA SER  356      27.778  28.249  11.625  1.00 31.10      B3
ATOM  2480 CB SER  356      26.401  28.147  11.016  1.00 35.23      B3
ATOM  2481 OG SER  356      25.679  29.380  10.905  1.00 43.82      B3
ATOM  2482 HG SER  356      26.250  30.004  10.429  1.00  0.00      B3
ATOM  2483 C  SER  356      27.763  29.098  12.901  1.00 29.75      B3
ATOM  2484 O  SER  356      28.115  30.289  12.898  1.00 28.35      B3
ATOM  2485 N  HIS  357      27.465  28.464  14.025  1.00 27.82      B3
ATOM  2486 H  HIS  357      27.301  27.498  14.019  1.00  0.00      B3
ATOM  2487 CA HIS  357      27.434  29.194  15.259  1.00 26.58      B3
ATOM  2488 CB HIS  357      26.735  28.365  16.305  1.00 25.77      B3
ATOM  2489 CG HIS  357      25.219  28.360  16.063  1.00 27.67      B3
ATOM  2490 CD2 HIS  357     24.563  28.767  14.915  1.00 28.94      B3
ATOM  2491 ND1 HIS  357     24.277  27.963  16.915  1.00 28.43      B3
ATOM  2492 HD1 HIS  357     24.456  27.622  17.828  1.00  0.00      B3
ATOM  2493 CE1 HIS  357     23.112  28.103  16.337  1.00 28.64      B3
ATOM  2494 NE2 HIS  357     23.298  28.589  15.130  1.00 29.48      B3
ATOM  2495 HE2 HIS  357     22.576  28.801  14.495  1.00  0.00      B3
ATOM  2496 C  HIS  357      28.852  29.506  15.645  1.00 27.93      B3
ATOM  2497 O  HIS  357      29.119  30.606  16.115  1.00 29.15      B3

ATOM  2498 N  LEU  358      29.830  28.637  15.383  1.00 28.33      B3
ATOM  2499 H  LEU  358      29.624  27.761  14.997  1.00  0.00      B3
ATOM  2500 CA LEU  358      31.211  28.940  15.721  1.00 26.39      B3
ATOM  2501 CB LEU  358      32.030  27.702  15.547  1.00 21.42      B3
ATOM  2502 CG LEU  358      33.457  27.878  15.734  1.00 20.42      B3
ATOM  2503 CD1 LEU  358     33.805  28.078  17.165  1.00 16.79      B3
ATOM  2504 CD2 LEU  358     34.075  26.714  15.072  1.00 22.89      B3
ATOM  2505 C  LEU  358      31.721  30.067  14.822  1.00 26.45      B3
ATOM  2506 O  LEU  358      32.372  30.939  15.378  1.00 27.12      B3
ATOM  2507 N  GLN  359      31.460  30.130  13.518  1.00 29.11      B3
ATOM  2508 H  GLN  359      31.048  29.337  13.114  1.00  0.00      B3
ATOM  2509 CA GLN  359      31.863  31.254  12.671  1.00 29.10      B3
ATOM  2510 CB GLN  359      31.204  31.209  11.292  1.00 30.49      B3
ATOM  2511 CG GLN  359      31.395  29.952  10.455  1.00 38.14      B3
ATOM  2512 CD GLN  359      32.842  29.636  10.091  1.00 42.09      B3
ATOM  2513 OE1 GLN  359     33.774  29.979  10.821  1.00 46.15      B3
ATOM  2514 NE2 GLN  359     33.103  28.987   8.967  1.00 41.34      B3
ATOM  2515 HE21 GLN  359    32.341  28.706   8.412  1.00  0.00      B3
ATOM  2516 HE22 GLN  359    34.039  28.838   8.740  1.00  0.00      B3
ATOM  2517 C  GLN  359      31.512  32.621  13.254  1.00 29.89      B3
ATOM  2518 O  GLN  359      32.427  33.427  13.484  1.00 30.06      B3
ATOM  2519 N  SER  360      30.203  32.810  13.528  1.00 28.66      B3
ATOM  2520 H  SER  360      29.595  32.061  13.343  1.00  0.00      B3
ATOM  2521 CA SER  360      29.570  34.003  14.071  1.00 27.32      B3
ATOM  2522 CB SER  360      28.121  33.761  14.336  1.00 26.70      B3
ATOM  2523 OG SER  360      27.439  33.539  13.098  1.00 29.72      B3
ATOM  2524 HG SER  360      26.637  33.112  13.288  1.00  0.00      B3
ATOM  2525 C  SER  360      30.202  34.387  15.353  1.00 27.15      B3
ATOM  2526 O  SER  360      30.575  35.550  15.498  1.00 26.93      B3
ATOM  2527 N  PHE  361      30.383  33.403  16.246  1.00 25.58      B3
ATOM  2528 H  PHE  361      30.055  32.499  16.040  1.00  0.00      B3
ATOM  2529 CA PHE  361      31.066  33.626  17.517  1.00 25.20      B3
ATOM  2530 CB PHE  361      31.092  32.335  18.302  1.00 23.80      B3
ATOM  2531 CG PHE  361      31.796  32.394  19.655  1.00 23.63      B3
ATOM  2532 CD1 PHE  361     31.127  32.854  20.777  1.00 22.44      B3
ATOM  2533 CD2 PHE  361     33.098  31.931  19.770  1.00 23.35      B3
ATOM  2534 CE1 PHE  361     31.772  32.834  22.000  1.00 24.78      B3
ATOM  2535 CE2 PHE  361     33.719  31.921  21.002  1.00 21.26      B3
ATOM  2536 CZ PHE  361      33.058  32.368  22.114  1.00 19.54      B3
ATOM  2537 C  PHE  361      32.505  34.143  17.385  1.00 26.56      B3
ATOM  2538 O  PHE  361      32.914  34.979  18.183  1.00 26.76      B3
ATOM  2539 N  LEU  362      33.309  33.645  16.441  1.00 28.17      B3
ATOM  2540 H  LEU  362      32.962  32.921  15.874  1.00  0.00      B3
ATOM  2541 CA LEU  362      34.679  34.089  16.272  1.00 28.09      B3
ATOM  2542 CB LEU  362      35.452  33.125  15.338  1.00 28.38      B3
ATOM  2543 CG LEU  362      35.603  31.656  15.781  1.00 29.61      B3
ATOM  2544 CD1 LEU  362     36.306  30.996  14.633  1.00 31.65      B3
ATOM  2545 CD2 LEU  362     36.374  31.453  17.055  1.00 26.38      B3
ATOM  2546 C  LEU  362      34.692  35.449  15.536  1.00 29.18      B3
ATOM  2547 O  LEU  362      35.649  36.202  15.748  1.00 27.43      B3
ATOM  2548 N  GLU  363      33.664  35.763  14.710  1.00 29.54      B3
```

FIGURE 5

```
ATOM  2549 H  GLU  363      33.009  ...066  14.495  1.00  0.00      B3
ATOM  2550 CA GLU  363      33.496  37.090  14.145  1.00 30.30      B3
ATOM  2551 CB GLU  363      32.357  37.147  13.228  1.00 30.90      B3
ATOM  2552 CG GLU  363      32.763  36.735  11.849  1.00 38.69      B3
ATOM  2553 CD GLU  363      33.642  37.662  11.013  1.00 42.62      B3
ATOM  2554 OE1 GLU  363     33.896  37.282   9.860  1.00 46.58      B3
ATOM  2555 OE2 GLU  363     34.051  38.734  11.488  1.00 46.47      B3
ATOM  2556 C  GLU  363      33.229  38.098  15.246  1.00 30.19      B3
ATOM  2557 O  GLU  363      33.837  39.167  15.239  1.00 30.26      B3
ATOM  2558 N  VAL  364      32.397  37.726  16.217  1.00 30.04      B3
ATOM  2559 H  VAL  364      31.888  36.898  16.100  1.00  0.00      B3
ATOM  2560 CA VAL  364      32.178  38.572  17.400  1.00 31.90      B3
ATOM  2561 CB VAL  364      31.014  38.021  18.269  1.00 31.41      B3
ATOM  2562 CG1 VAL  364     30.860  38.811  19.562  1.00 30.73      B3
ATOM  2563 CG2 VAL  364     29.750  38.200  17.497  1.00 29.96      B3
ATOM  2564 C  VAL  364      33.402  38.493  18.275  1.00 35.89      B3
ATOM  2565 O  VAL  364      33.683  39.535  18.855  1.00 37.54      B3
ATOM  2566 N  SER  365      34.173  37.421  18.477  1.00 38.25      B3
ATOM  2567 H  SER  365      33.971  36.577  18.030  1.00  0.00      B3
ATOM  2568 CA SER  365      35.337  37.478  19.375  1.00 39.61      B3
ATOM  2569 CB SER  365      36.041  36.113  19.555  1.00 43.00      B3
ATOM  2570 OG SER  365      35.201  34.953  19.575  1.00 46.29      B3
ATOM  2571 HG SER  365      34.270  35.189  19.644  1.00  0.00      B3
ATOM  2572 C  SER  365      36.398  38.418  18.840  1.00 38.21      B3
ATOM  2573 O  SER  365      37.103  38.099  17.902  1.00 36.91      B3
ATOM  2574 N  TYR  366      36.575  38.540  17.514  1.00 38.00      B3
ATOM  2575 H  TYR  366      36.079  37.945  16.910  1.00  0.00      B3
ATOM  2576 CA TYR  366      37.568  39.463  16.969  1.00 41.85      B3
ATOM  2577 CB TYR  366      37.778  39.330  15.436  1.00 38.53      B3
ATOM  2578 CG TYR  366      38.662  40.447  14.879  1.00 38.21      B3
ATOM  2579 CD1 TYR  366     38.104  41.464  14.129  1.00 37.18      B3
ATOM  2580 CE1 TYR  366     38.918  42.495  13.678  1.00 41.77      B3
ATOM  2581 CD2 TYR  366     40.041  40.443  15.182  1.00 40.21      B3
ATOM  2582 CE2 TYR  366     40.849  41.466  14.739  1.00 40.76      B3
ATOM  2583 CZ TYR  366      40.297  42.504  13.976  1.00 42.82      B3
ATOM  2584 OH TYR  366      41.151  43.522  13.493  1.00 41.30      B3
ATOM  2585 HH TYR  366      40.743  43.977  12.755  1.00  0.00      B3
ATOM  2586 C  TYR  366      37.133  40.893  17.241  1.00 40.55      B3
ATOM  2587 O  TYR  366      37.917  41.647  17.798  1.00 40.92      B3
ATOM  2588 N  ARG  367      35.933  41.309  16.853  1.00 41.88      B3
ATOM  2589 H  ARG  367      35.360  40.682  16.360  1.00  0.00      B3
ATOM  2590 CA ARG  367      35.442  42.653  17.139  1.00 43.32      B3
ATOM  2591 CB ARG  367      34.013  42.709  16.650  1.00 46.82      B3
ATOM  2592 CG ARG  367      33.528  44.130  16.650  1.00 56.74      B3
ATOM  2593 CD ARG  367      32.069  44.267  16.248  1.00 61.81      B3
ATOM  2594 NE ARG  367      31.723  45.687  16.229  1.00 66.59      B3
ATOM  2595 HE ARG  367      32.438  46.356  16.172  1.00  0.00      B3
ATOM  2596 CZ ARG  367      30.458  46.091  16.308  1.00 69.75      B3
ATOM  2597 NH1 ARG  367     29.448  45.220  16.413  1.00 72.65      B3
ATOM  2598 HH11 ARG  367    29.631  44.236  16.410  1.00  0.00      B3
ATOM  2599 HH12 ARG  367    28.503  45.548  16.445  1.00  0.00      B3

ATOM  2600 NH2 ARG  367     30.160  47.375  16.162  1.00 71.04      B3
ATOM  2601 HH21 ARG  367    29.204  47.665  16.222  1.00  0.00      B3
ATOM  2602 HH22 ARG  367    30.888  48.043  16.013  1.00  0.00      B3
ATOM  2603 C  ARG  367      35.551  43.011  18.615  1.00 40.96      B3
ATOM  2604 O  ARG  367      35.994  44.090  19.012  1.00 41.10      B3
ATOM  2605 N  VAL  368      35.162  42.135  19.542  1.00 37.83      B3
ATOM  2606 H  VAL  368      34.726  41.316  19.217  1.00  0.00      B3
ATOM  2607 CA VAL  368      35.331  42.492  20.968  1.00 37.34      B3
ATOM  2608 CB VAL  368      34.748  41.043  21.664  1.00 35.75      B3
ATOM  2609 CG1 VAL  368     35.087  40.867  23.140  1.00 35.10      B3
ATOM  2610 CG2 VAL  368     33.259  41.230  21.586  1.00 33.28      B3
ATOM  2611 C  VAL  368      36.815  42.459  21.325  1.00 38.75      B3
ATOM  2612 O  VAL  368      37.144  43.498  21.777  1.00 40.11      B3
ATOM  2613 N  LEU  369      37.759  41.600  20.835  1.00 39.59      B3
ATOM  2614 H  LEU  369      37.492  40.818  20.308  1.00  0.00      B3
ATOM  2615 CA LEU  369     39.180  41.780  21.148  1.00 40.05      B3
ATOM  2616 CB LEU  369     39.984  40.601  20.679  1.00 37.15      B3
ATOM  2617 CG LEU  369     39.831  39.335  21.426  1.00 37.54      B3
ATOM  2618 CD1 LEU  369     40.349  38.238  20.528  1.00 39.70      B3
ATOM  2619 CD2 LEU  369     40.563  39.394  22.747  1.00 36.86      B3
ATOM  2620 C  LEU  369      39.817  43.031  20.542  1.00 41.88      B3
ATOM  2621 O  LEU  369      40.711  43.654  21.144  1.00 41.30      B3
ATOM  2622 N  ARG  370      39.333  43.413  19.354  1.00 42.80      B3
ATOM  2623 H  ARG  370      38.619  42.884  18.957  1.00  0.00      B3
ATOM  2624 CA ARG  370     39.819  44.577  18.663  1.00 44.46      B3
ATOM  2625 CB ARG  370     39.184  44.569  17.316  1.00 42.06      B3
ATOM  2626 CG ARG  370     39.424  45.719  16.371  1.00 43.93      B3
ATOM  2627 CD ARG  370     40.894  45.910  16.169  1.00 45.57      B3
ATOM  2628 NE ARG  370     41.219  46.681  14.976  1.00 48.00      B3
ATOM  2629 HE ARG  370     40.524  46.867  14.312  1.00  0.00      B3
ATOM  2630 CZ ARG  370     42.469  47.153  14.791  1.00 48.45      B3
ATOM  2631 NH1 ARG  370    43.443  46.961  15.691  1.00 49.13      B3
ATOM  2632 HH11 ARG  370    43.262  46.456  16.534  1.00 0.00      B3
ATOM  2633 HH12 ARG  370    44.357  47.326  15.520  1.00 0.00      B3
ATOM  2634 NH2 ARG  370     42.821  47.710  13.635  1.00 48.59      B3
ATOM  2635 HH21 ARG  370    42.163  47.785  12.989  1.00 0.00      B3
ATOM  2636 HH22 ARG  370    43.751  48.057  13.516  1.00 0.00      B3
ATOM  2637 C  ARG  370      39.386  45.740  19.558  1.00 49.12      B3
ATOM  2638 O  ARG  370      40.216  46.615  19.926  1.00 49.67      B3
ATOM  2639 N  HIS  371      38.162  45.728  20.123  1.00 52.80      B3
ATOM  2640 H  HIS  371      37.581  44.955  19.949  1.00 0.00       B3
ATOM  2641 CA HIS  371     37.745  46.738  21.080  1.00 56.45      B3
ATOM  2642 CB HIS  371     36.284  46.604  21.459  1.00 62.15      B3
ATOM  2643 CG HIS  371     35.320  46.991  20.346  1.00 71.70      B3
ATOM  2644 CD2 HIS  371    35.596  47.877  19.313  1.00 75.03      B3
ATOM  2645 ND1 HIS  371    34.067  46.546  20.106  1.00 75.91      B3
ATOM  2646 HD1 HIS  371    33.594  45.897  20.732  1.00 0.00       B3
ATOM  2647 CE1 HIS  371    33.580  47.116  19.077  1.00 77.90      B3
ATOM  2648 NE2 HIS  371    34.507  47.914  18.573  1.00 77.52      B3
ATOM  2649 HE2 HIS  371    34.401  48.460  17.764  1.00 0.00       B3
ATOM  2650 C  HIS  371      38.533  46.469  22.387  1.00 51.97      B3
```

FIGURE 5

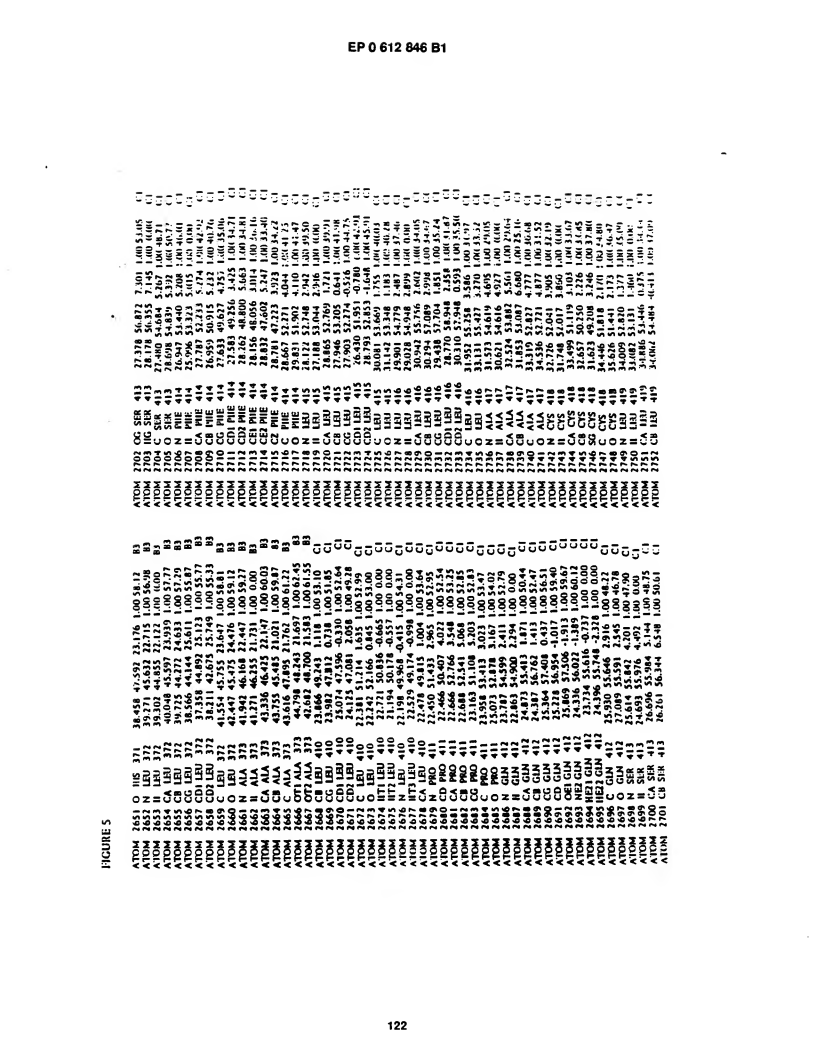


FIGURE 5

```
ATOM  2753 CG  LEU  419      32.866  5..453  -1.244  1.00 39.61      C1
ATOM  2754 CD1 LEU  419      31.866  54.918  -1.609  1.00 39.24      C1
ATOM  2755 CD2 LEU  419      33.349  53.207  -2.553  1.00 40.02      C1
ATOM  2756 C   LEU  419      36.102  54.041   1.047  1.00 32.33      C1
ATOM  2757 O   LEU  419      37.198  53.973   0.549  1.00 31.60      C1
ATOM  2758 N   GLU  420      35.974  54.483   2.273  1.00 31.92      C1
ATOM  2759 H   GLU  420      35.068  54.528   2.648  1.00  0.00      C1
ATOM  2760 CA  GLU  420      37.078  54.905   3.092  1.00 31.79      C1
ATOM  2761 CB  GLU  420      36.477  55.462   4.344  1.00 34.29      C1
ATOM  2762 CG  GLU  420      37.430  56.240   5.185  1.00 38.66      C1
ATOM  2763 CD  GLU  420      36.952  56.499   6.609  1.00 45.20      C1
ATOM  2764 OE1 GLU  420      37.873  56.849   7.367  1.00 45.67      C1
ATOM  2765 OE2 GLU  420      35.745  56.345   6.954  1.00 44.21      C1
ATOM  2766 C   GLU  420      38.043  53.763   3.423  1.00 31.87      C1
ATOM  2767 O   GLU  420      39.253  53.949   3.270  1.00 32.82      C1
ATOM  2768 N   GLN  421      37.553  52.624   3.954  1.00 30.46      C1
ATOM  2769 H   GLN  421      36.583  52.556   4.098  1.00  0.00      C1
ATOM  2770 CA  GLN  421      38.366  51.461   4.283  1.00 29.34      C1
ATOM  2771 CB  GLN  421      37.545  50.389   4.984  1.00 30.88      C1
ATOM  2772 CG  GLN  421      37.308  50.634   6.463  1.00 33.58      C1
ATOM  2773 CD  GLN  421      36.320  49.625   7.058  1.00 37.89      C1
ATOM  2774 OE1 GLN  421      35.357  49.236   6.398  1.00 43.18      C1
ATOM  2775 NE2 GLN  421      36.427  49.095   8.275  1.00 37.13      C1
ATOM  2776 HE21 GLN  421      35.695  48.505   8.556  1.00  0.00      C1
ATOM  2777 HE22 GLN  421      37.207  49.330   8.812  1.00  0.00      C1
ATOM  2778 C   GLN  421      38.991  50.862   3.026  1.00 27.32      C1
ATOM  2779 O   GLN  421      40.152  50.445   3.099  1.00 29.09      C1
ATOM  2780 N   VAL  422      38.379  50.845   1.847  1.00 23.57      C1
ATOM  2781 H   VAL  422      37.448  51.138   1.803  1.00  0.00      C1
ATOM  2782 CA  VAL  422      39.077  50.420   0.651  1.00 23.52      C1
ATOM  2783 CB  VAL  422      38.163  50.636  -0.556  1.00 22.67      C1
ATOM  2784 CG1 VAL  422      38.873  50.455  -1.868  1.00 21.56      C1
ATOM  2785 CG2 VAL  422      37.057  49.610  -0.465  1.00 26.79      C1
ATOM  2786 C   VAL  422      40.353  51.256   0.514  1.00 26.27      C1
ATOM  2787 O   VAL  422      41.458  50.708   0.508  1.00 28.77      C1
ATOM  2788 N   ARG  423      40.275  52.599   0.575  1.00 27.49      C1
ATOM  2789 H   ARG  423      39.402  53.016   0.735  1.00  0.00      C1
ATOM  2790 CA  ARG  423      41.436  53.456   0.346  1.00 25.91      C1
ATOM  2791 CB  ARG  423      41.098  54.943   0.312  1.00 24.39      C1
ATOM  2792 CG  ARG  423      40.167  55.366  -0.807  1.00 22.81      C1
ATOM  2793 CD  ARG  423      40.525  54.798  -2.172  1.00 25.55      C1
ATOM  2794 NE  ARG  423      39.707  55.387  -3.216  1.00 25.38      C1
ATOM  2795 HE  ARG  423      39.168  56.173  -2.989  1.00  0.00      C1
ATOM  2796 CZ  ARG  423      39.629  54.928  -4.466  1.00 27.32      C1
ATOM  2797 NH1 ARG  423      40.264  53.857  -4.949  1.00 26.37      C1
ATOM  2798 HH11 ARG  423      40.884  53.341  -4.365  1.00  0.00      C1
ATOM  2799 HH12 ARG  423      40.150  53.595  -5.907  1.00  0.00      C1
ATOM  2800 NH2 ARG  423      38.960  55.682  -5.325  1.00 30.38      C1
ATOM  2801 HH21 ARG  423      38.539  56.537  -5.023  1.00  0.00      C1
ATOM  2802 HH22 ARG  423      38.865  55.385  -6.275  1.00  0.00      C1
ATOM  2803 C   ARG  423      42.429  53.241   1.432  1.00 23.60      C1
ATOM  2804 O   ARG  423      43.594  53.147   1.127  1.00 24.37      C1
ATOM  2805 N   LYS  424      42.065  53.050   2.668  1.00 24.38      C1
ATOM  2806 H   LYS  424      41.109  53.051   2.890  1.00  0.00      C1
ATOM  2807 CA  LYS  424      43.043  52.855   3.721  1.00 25.12      C1
ATOM  2808 CB  LYS  424      42.352  52.791   5.051  1.00 27.89      C1
ATOM  2809 CG  LYS  424      43.312  52.936   6.190  1.00 28.56      C1
ATOM  2810 CD  LYS  424      42.579  52.580   7.486  1.00 35.51      C1
ATOM  2811 CE  LYS  424      41.338  53.425   7.853  1.00 40.34      C1
ATOM  2812 NZ  LYS  424      40.519  52.722   8.884  1.00 42.14      C1
ATOM  2813 HZ1 LYS  424      41.079  52.559   9.695  1.00  0.00      C1
ATOM  2814 HZ2 LYS  424      40.208  51.814   8.435  1.00  0.00      C1
ATOM  2815 HZ3 LYS  424      39.689  53.306   9.065  1.00  0.00      C1
ATOM  2816 C   LYS  424      43.761  51.547   3.462  1.00 27.10      C1
ATOM  2817 O   LYS  424      44.923  51.425   3.848  1.00 30.64      C1
ATOM  2818 N   ILE  425      43.190  50.542   2.794  1.00 26.85      C1
ATOM  2819 H   ILE  425      42.260  50.607   2.488  1.00  0.00      C1
ATOM  2820 CA  ILE  425      43.949  49.312   2.561  1.00 25.46      C1
ATOM  2821 CB  ILE  425      42.965  48.093   2.336  1.00 24.91      C1
ATOM  2822 CG2 ILE  425      43.654  46.786   1.995  1.00 22.01      C1
ATOM  2823 CG1 ILE  425      42.229  47.909   3.633  1.00 25.84      C1
ATOM  2824 CD  ILE  425      40.885  47.169   3.412  1.00 25.92      C1
ATOM  2825 C   ILE  425      44.824  49.549   1.346  1.00 23.84      C1
ATOM  2826 O   ILE  425      45.959  49.069   1.316  1.00 24.57      C1
ATOM  2827 N   GLN  426      44.361  50.267   0.323  1.00 23.28      C1
ATOM  2828 H   GLN  426      43.501  50.630   0.593  1.00  0.00      C1
ATOM  2829 CA  GLN  426      45.164  50.531  -0.871  1.00 24.13      C1
ATOM  2830 CB  GLN  426      44.421  51.344  -1.896  1.00 24.04      C1
ATOM  2831 CG  GLN  426      43.275  50.539  -2.396  1.00 23.56      C1
ATOM  2832 CD  GLN  426      42.466  51.311  -3.511  1.00 25.92      C1
ATOM  2833 OE1 GLN  426      41.704  52.047  -3.345  1.00 25.54      C1
ATOM  2834 NE2 GLN  426      42.337  50.509  -4.672  1.00 27.55      C1
ATOM  2835 HE21 GLN  426      41.755  50.948  -5.323  1.00  0.00      C1
ATOM  2836 HE22 GLN  426      42.850  49.696  -4.853  1.00  0.00      C1
ATOM  2837 C   GLN  426      46.404  51.312  -0.488  1.00 26.69      C1
ATOM  2838 O   GLN  426      47.486  51.109  -1.046  1.00 29.73      C1
ATOM  2839 N   GLY  427      46.300  52.204   0.499  1.00 26.49      C1
ATOM  2840 H   GLY  427      45.410  52.414   0.854  1.00  0.00      C1
ATOM  2841 CA  GLY  427      47.446  52.894   1.022  1.00 24.25      C1
ATOM  2842 C   GLY  427      48.467  51.913   1.589  1.00 23.08      C1
ATOM  2843 O   GLY  427      49.597  51.921   1.106  1.00 22.28      C1
ATOM  2844 N   ASP  428      48.107  51.073   2.575  1.00 22.75      C1
ATOM  2845 H   ASP  428      47.189  51.111   2.918  1.00  0.00      C1
ATOM  2846 CA  ASP  428      49.039  50.108   3.131  1.00 23.87      C1
ATOM  2847 CB  ASP  428      48.415  49.199   4.117  1.00 26.52      C1
ATOM  2848 CG  ASP  428      47.437  49.779   5.097  1.00 28.84      C1
ATOM  2849 OD1 ASP  428      46.420  49.151   5.265  1.00 31.81      C1
ATOM  2850 OD2 ASP  428      47.662  50.804   5.716  1.00 30.77      C1
ATOM  2851 C   ASP  428      49.676  49.191   2.063  1.00 24.16      C1
ATOM  2852 O   ASP  428      50.812  48.896   2.088  1.00 26.17      C1
ATOM  2853 N   GLY  429      48.840  48.822   1.069  1.00 23.01      C1
ATOM  2854 H   GLY  429      47.905  49.113   1.071  1.00  0.00      C1
```

FIGURE 5

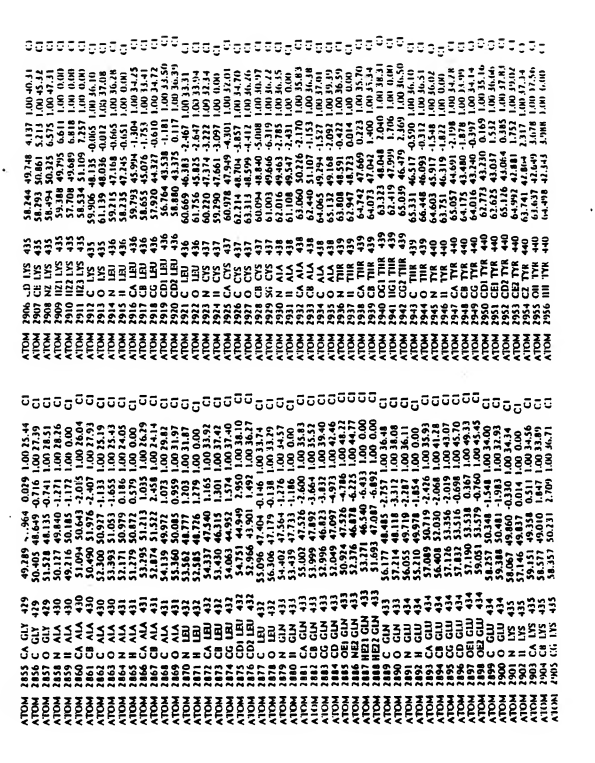


FIGURE 5

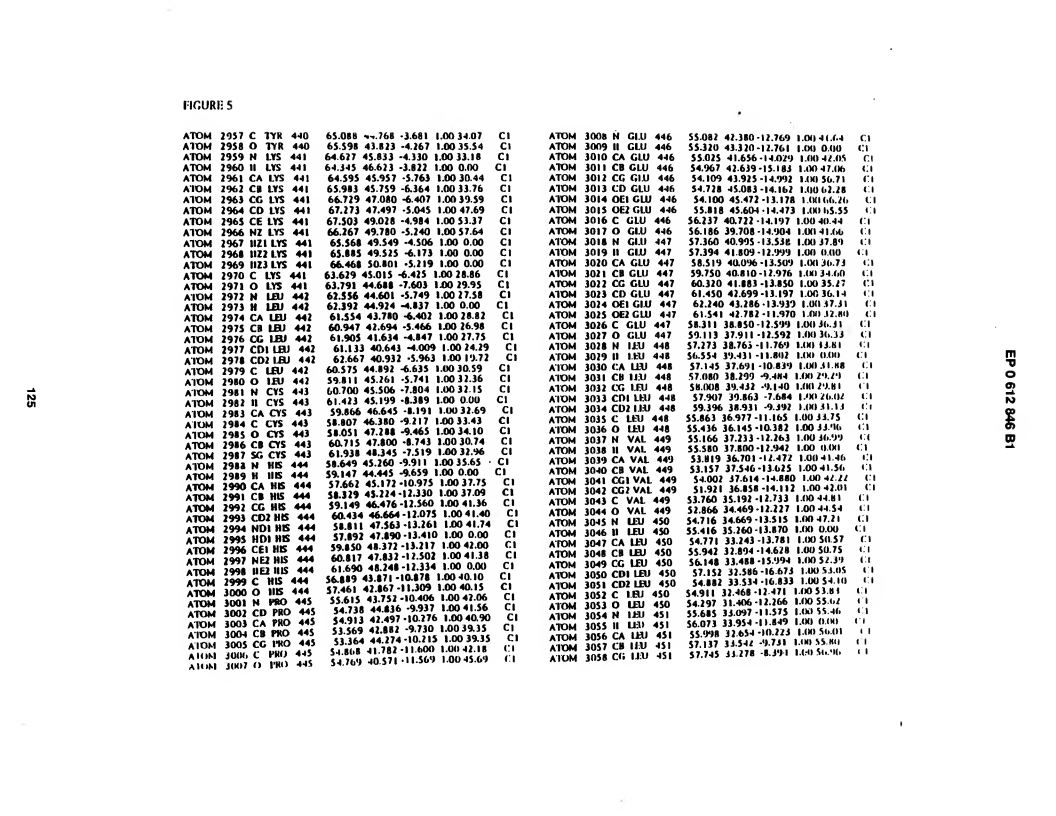

ATOM 2957 C TYR 440 65.088 -3.768 -3.681 1.00 34.07 C1
ATOM 2958 O TYR 440 65.598 43.823 -4.267 1.00 35.54 C1
ATOM 2959 N LYS 441 64.627 45.853 -4.330 1.00 33.18 C1
ATOM 2960 H LYS 441 64.345 46.623 -3.822 1.00 0.00 C1
ATOM 2961 CA LYS 441 64.595 45.957 -5.763 1.00 30.44 C1
ATOM 2962 CB LYS 441 65.983 45.759 -6.364 1.00 33.76 C1
ATOM 2963 CG LYS 441 66.729 47.080 -6.407 1.00 39.59 C1
ATOM 2964 CD LYS 441 67.273 47.497 -5.045 1.00 47.69 C1
ATOM 2965 CE LYS 441 67.502 49.028 -4.987 1.00 53.35 C1
ATOM 2966 NZ LYS 441 66.267 49.780 -5.240 1.00 57.64 C1
ATOM 2967 HZ1 LYS 441 65.568 49.549 -4.506 1.00 0.00 C1
ATOM 2968 HZ2 LYS 441 65.885 49.525 -6.173 1.00 0.00 C1
ATOM 2969 HZ3 LYS 441 66.468 50.801 -5.219 1.00 0.00 C1
ATOM 2970 C LYS 441 63.629 45.015 -6.425 1.00 28.86 C1
ATOM 2971 O LYS 441 63.791 44.688 -7.603 1.00 29.95 C1
ATOM 2972 N LEU 442 62.556 44.601 -5.749 1.00 27.58 C1
ATOM 2973 H LEU 442 62.392 44.924 -4.837 1.00 0.00 C1
ATOM 2974 CA LEU 442 61.554 43.780 -6.402 1.00 28.82 C1
ATOM 2975 CB LEU 442 60.947 42.694 -5.466 1.00 26.98 C1
ATOM 2976 CG LEU 442 61.905 41.634 -4.847 1.00 27.75 C1
ATOM 2977 CD1 LEU 442 61.133 40.647 -4.009 1.00 24.29 C1
ATOM 2978 CD2 LEU 442 62.667 40.932 -5.963 1.00 19.72 C1
ATOM 2979 C LEU 442 60.575 44.892 -6.635 1.00 30.59 C1
ATOM 2980 O LEU 442 59.811 45.261 -5.741 1.00 32.36 C1
ATOM 2981 N CYS 443 60.700 45.506 -7.804 1.00 32.15 C1
ATOM 2982 H CYS 443 61.423 45.199 -8.389 1.00 0.00 C1
ATOM 2983 CA CYS 443 59.866 46.645 -8.191 1.00 32.69 C1
ATOM 2984 C CYS 443 58.807 46.380 -9.217 1.00 33.43 C1
ATOM 2985 O CYS 443 58.051 47.288 -9.465 1.00 34.10 C1
ATOM 2986 CB CYS 443 60.715 47.800 -8.743 1.00 30.74 C1
ATOM 2987 SG CYS 443 61.938 48.345 -7.519 1.00 32.96 C1
ATOM 2988 N HIS 444 58.649 45.260 -9.911 1.00 35.65 C1
ATOM 2989 H HIS 444 59.147 44.445 -9.659 1.00 0.00 C1
ATOM 2990 CA HIS 444 57.662 45.172 -10.975 1.00 37.75 C1
ATOM 2991 CB HIS 444 58.329 45.224 -12.330 1.00 37.09 C1
ATOM 2992 CG HIS 444 59.149 46.476 -12.560 1.00 41.36 C1
ATOM 2993 CD2 HIS 444 60.434 46.664 -12.075 1.00 41.40 C1
ATOM 2994 ND1 HIS 444 58.811 47.563 -13.261 1.00 41.74 C1
ATOM 2995 HD1 HIS 444 57.892 47.890 -13.410 1.00 0.00 C1
ATOM 2996 CE1 HIS 444 59.850 48.372 -13.317 1.00 42.00 C1
ATOM 2997 NE2 HIS 444 60.817 47.832 -12.502 1.00 41.38 C1
ATOM 2998 HE2 HIS 444 61.690 48.248 -12.334 1.00 0.00 C1
ATOM 2999 C HIS 444 56.889 43.871 -10.878 1.00 40.10 C1
ATOM 3000 O HIS 444 57.461 42.867 -11.309 1.00 40.15 C1
ATOM 3001 N PRO 445 55.615 43.752 -10.406 1.00 42.06 C1
ATOM 3002 CD PRO 445 54.738 44.836 -9.937 1.00 41.56 C1
ATOM 3003 CA PRO 445 54.913 42.497 -10.276 1.00 40.90 C1
ATOM 3004 CB PRO 445 53.569 42.882 -9.730 1.00 39.35 C1
ATOM 3005 CG PRO 445 53.364 44.274 -10.215 1.00 39.35 C1
ATOM 3006 C PRO 445 54.868 41.782 -11.600 1.00 42.18 C1
ATOM 3007 O PRO 445 54.769 40.571 -11.569 1.00 45.69 C1
ATOM 3008 N GLU 446 55.082 42.380 -12.769 1.00 41.64 C1
ATOM 3009 H GLU 446 55.320 43.320 -12.761 1.00 0.00 C1
ATOM 3010 CA GLU 446 55.025 41.656 -14.029 1.00 42.05 C1
ATOM 3011 CB GLU 446 54.967 42.639 -15.185 1.00 47.06 C1
ATOM 3012 CG GLU 446 54.109 43.923 -14.992 1.00 56.71 C1
ATOM 3013 CD GLU 446 54.728 45.083 -14.162 1.00 62.28 C1
ATOM 3014 OE1 GLU 446 54.100 45.472 -13.178 1.00 66.26 C1
ATOM 3015 OE2 GLU 446 55.818 45.604 -14.473 1.00 65.55 C1
ATOM 3016 C GLU 446 56.237 40.722 -14.197 1.00 40.44 C1
ATOM 3017 O GLU 446 56.186 39.708 -14.904 1.00 41.66 C1
ATOM 3018 N GLU 447 57.360 40.995 -13.538 1.00 37.89 C1
ATOM 3019 H GLU 447 57.394 41.809 -12.999 1.00 0.00 C1
ATOM 3020 CA GLU 447 58.519 40.096 -13.509 1.00 36.73 C1
ATOM 3021 CB GLU 447 59.750 40.810 -12.976 1.00 34.60 C1
ATOM 3022 CG GLU 447 60.320 41.883 -13.850 1.00 35.27 C1
ATOM 3023 CD GLU 447 61.450 42.699 -13.197 1.00 36.14 C1
ATOM 3024 OE1 GLU 447 62.240 43.286 -13.939 1.00 37.31 C1
ATOM 3025 OE2 GLU 447 61.541 42.782 -11.970 1.00 32.80 C1
ATOM 3026 C GLU 447 58.311 38.850 -12.599 1.00 36.31 C1
ATOM 3027 O GLU 447 59.113 37.911 -12.592 1.00 36.33 C1
ATOM 3028 N LEU 448 57.273 38.765 -11.769 1.00 33.81 C1
ATOM 3029 H LEU 448 56.554 39.431 -11.802 1.00 0.00 C1
ATOM 3030 CA LEU 448 57.145 37.691 -10.839 1.00 31.88 C1
ATOM 3031 CB LEU 448 57.080 38.299 -9.484 1.00 29.25 C1
ATOM 3032 CG LEU 448 58.008 39.432 -9.140 1.00 29.81 C1
ATOM 3033 CD1 LEU 448 57.907 39.863 -7.684 1.00 26.02 C1
ATOM 3034 CD2 LEU 448 59.396 38.931 -9.392 1.00 31.13 C1
ATOM 3035 C LEU 448 55.863 36.977 -11.165 1.00 31.62 C1
ATOM 3036 O LEU 448 55.436 36.145 -10.382 1.00 33.96 C1
ATOM 3037 N VAL 449 55.166 37.233 -12.263 1.00 30.99 C1
ATOM 3038 H VAL 449 55.580 37.800 -12.942 1.00 0.00 C1
ATOM 3039 CA VAL 449 53.819 36.701 -12.472 1.00 31.46 C1
ATOM 3040 CB VAL 449 53.157 37.546 -13.625 1.00 41.56 C1
ATOM 3041 CG1 VAL 449 54.002 37.614 -14.880 1.00 42.22 C1
ATOM 3042 CG2 VAL 449 51.921 36.858 -14.112 1.00 44.01 C1
ATOM 3043 C VAL 449 53.760 35.192 -12.733 1.00 44.81 C1
ATOM 3044 O VAL 449 52.866 34.469 -12.227 1.00 44.54 C1
ATOM 3045 N LEU 450 54.716 34.669 -13.515 1.00 47.21 C1
ATOM 3046 H LEU 450 55.416 35.260 -13.870 1.00 0.00 C1
ATOM 3047 CA LEU 450 54.771 33.243 -13.781 1.00 50.57 C1
ATOM 3048 CB LEU 450 55.942 32.894 -14.628 1.00 50.75 C1
ATOM 3049 CG LEU 450 56.148 33.488 -15.994 1.00 52.39 C1
ATOM 3050 CD1 LEU 450 57.152 32.598 -16.673 1.00 54.05 C1
ATOM 3051 CD2 LEU 450 54.882 33.534 -16.833 1.00 54.10 C1
ATOM 3052 C LEU 450 54.911 32.468 -12.471 1.00 53.81 C1
ATOM 3053 O LEU 450 54.297 31.406 -12.266 1.00 55.62 C1
ATOM 3054 N LEU 451 55.685 33.097 -11.575 1.00 55.46 C1
ATOM 3055 H LEU 451 56.073 33.954 -11.849 1.00 0.00 C1
ATOM 3056 CA LEU 451 55.998 32.654 -10.223 1.00 56.01 C1
ATOM 3057 CB LEU 451 57.137 33.542 -9.733 1.00 55.80 C1
ATOM 3058 CG LEU 451 57.745 33.278 -8.391 1.00 56.96 C1

FIGURE 5

```
ATOM  3059 CD1 LEU  451      58.833  ...284  -8.653  1.00 59.12      C1
ATOM  3060 CD2 LEU  451      58.369  34.511  -7.751  1.00 58.27      C1
ATOM  3061 C   LEU  451      54.785  32.700  -9.280  1.00 55.96      C1
ATOM  3062 O   LEU  451      54.717  31.935  -8.319  1.00 53.74      C1
ATOM  3063 N   GLY  452      53.774  33.533  -9.522  1.00 57.52      C1
ATOM  3064 H   GLY  452      53.889  34.741 -10.191  1.00  0.00      C1
ATOM  3065 CA  GLY  452      52.567  33.515  -8.710  1.00 60.66      C1
ATOM  3066 C   GLY  452      51.942  32.137  -8.772  1.00 63.64      C1
ATOM  3067 O   GLY  452      51.476  31.593  -7.782  1.00 62.60      C1
ATOM  3068 N   HIS  453      52.089  31.545  -9.969  1.00 68.46      C1
ATOM  3069 H   HIS  453      52.628  32.040 -10.618  1.00  0.00      C1
ATOM  3070 CA  HIS  453      51.606  30.205 -10.326  1.00 72.27      C1
ATOM  3071 CB  HIS  453      51.785  29.908 -11.828  1.00 73.84      C1
ATOM  3072 CG  HIS  453      51.421  31.061 -12.777  1.00 77.81      C1
ATOM  3073 CD2 HIS  453      50.599  32.148 -12.498  1.00 79.19      C1
ATOM  3074 ND1 HIS  453      51.886  31.244 -14.012  1.00 79.84      C1
ATOM  3075 HD1 HIS  453      52.617  30.739 -14.425  1.00  0.00      C1
ATOM  3076 CE1 HIS  453      51.385  32.382 -14.470  1.00 81.11      C1
ATOM  3077 NE2 HIS  453      50.613  32.923 -13.551  1.00 79.85      C1
ATOM  3078 HE2 HIS  453      50.230  33.825 -13.586  1.00  0.00      C1
ATOM  3079 C   HIS  453      52.454  29.235  -9.515  1.00 73.43      C1
ATOM  3080 O   HIS  453      51.875  28.531  -8.692  1.00 73.56      C1
ATOM  3081 N   SER  454      53.785  29.207  -9.651  1.00 74.64      C1
ATOM  3082 H   SER  454      54.214  29.739 -10.351  1.00  0.00      C1
ATOM  3083 CA  SER  454      54.639  28.411  -8.765  1.00 77.07      C1
ATOM  3084 CB  SER  454      56.123  28.762  -8.980  1.00 77.34      C1
ATOM  3085 OG  SER  454      57.095  27.715  -9.124  1.00 75.24      C1
ATOM  3086 HG  SER  454      57.149  27.211  -8.306  1.00  0.00      C1
ATOM  3087 C   SER  454      54.332  28.608  -7.262  1.00 78.84      C1
ATOM  3088 O   SER  454      54.270  27.617  -6.535  1.00 80.57      C1
ATOM  3089 N   LEU  455      54.070  29.789  -6.693  1.00 79.72      C1
ATOM  3090 H   LEU  455      53.956  30.582  -7.250  1.00  0.00      C1
ATOM  3091 CA  LEU  455      53.849  29.915  -5.257  1.00 80.43      C1
ATOM  3092 CB  LEU  455      54.085  31.347  -4.838  1.00 80.20      C1
ATOM  3093 CG  LEU  455      55.389  31.981  -5.269  1.00 81.67      C1
ATOM  3094 CD1 LEU  455      55.254  33.494  -5.419  1.00 81.36      C1
ATOM  3095 CD2 LEU  455      56.431  31.579  -4.264  1.00 82.26      C1
ATOM  3096 C   LEU  455      52.438  29.510  -4.848  1.00 81.56      C1
ATOM  3097 O   LEU  455      52.038  29.893  -3.741  1.00 82.72      C1
ATOM  3098 N   GLY  456      51.653  28.816  -5.708  1.00 81.89      C1
ATOM  3099 H   GLY  456      52.026  28.592  -6.584  1.00  0.00      C1
ATOM  3100 CA  GLY  456      50.269  28.361  -5.467  1.00 82.22      C1
ATOM  3101 C   GLY  456      49.220  29.386  -4.973  1.00 82.56      C1
ATOM  3102 O   GLY  456      48.268  28.989  -4.276  1.00 82.38      C1
ATOM  3103 N   ILE  457      49.342  30.697  -5.286  1.00 82.54      C1
ATOM  3104 H   ILE  457      50.075  30.942  -5.894  1.00  0.00      C1
ATOM  3105 CA  ILE  457      48.435  31.761  -4.824  1.00 81.63      C1
ATOM  3106 CB  ILE  457      49.110  33.157  -5.086  1.00 80.69      C1
ATOM  3107 CG2 ILE  457      48.218  34.305  -4.662  1.00 79.76      C1
ATOM  3108 CG1 ILE  457      50.369  33.275  -4.253  1.00 79.82      C1
ATOM  3109 CD ILE  457      51.506  33.868  -5.081  1.00 77.89      C1
ATOM  3110 C   ILE  457      47.048  31.698  -5.472  1.00 81.76      C1
ATOM  3111 O   ILE  457      46.903  31.761  -6.700  1.00 82.57      C1
ATOM  3112 N   PRO  458      45.963  31.583  -4.705  1.00 81.40      C1
ATOM  3113 CD  PRO  458      45.959  31.245  -3.278  1.00 81.71      C1
ATOM  3114 CA  PRO  458      44.607  31.643  -5.264  1.00 80.74      C1
ATOM  3115 CB  PRO  458      43.779  30.942  -4.157  1.00 81.14      C1
ATOM  3116 CG  PRO  458      44.757  30.293  -3.173  1.00 80.47      C1
ATOM  3117 C   PRO  458      44.120  33.063  -5.648  1.00 79.70      C1
ATOM  3118 O   PRO  458      43.674  33.736  -4.718  1.00 80.10      C1
ATOM  3119 N   TRP  459      44.171  33.662  -6.861  1.00 78.19      C1
ATOM  3120 H   TRP  459      44.614  33.185  -7.591  1.00  0.00      C1
ATOM  3121 CA  TRP  459      43.543  34.986  -7.092  1.00 77.73      C1
ATOM  3122 CB  TRP  459      43.802  35.428  -8.522  1.00 78.71      C1
ATOM  3123 CG  TRP  459      43.054  36.677  -9.017  1.00 81.27      C1
ATOM  3124 CD2 TRP  459      41.802  36.771  -9.618  1.00 82.89      C1
ATOM  3125 CE2 TRP  459      41.717  38.139  -9.883  1.00 84.21      C1
ATOM  3126 CE3 TRP  459      40.738  35.960  -9.983  1.00 84.48      C1
ATOM  3127 CD1 TRP  459      43.661  37.899  -8.925  1.00 83.89      C1
ATOM  3128 NE1 TRP  459      42.828  38.765  -9.460  1.00 85.23      C1
ATOM  3129 HE1 TRP  459      42.944  39.738  -9.483  1.00  0.00      C1
ATOM  3130 CZ2 TRP  459      40.615  38.727 -10.494  1.00 84.17      C1
ATOM  3131 CZ3 TRP  459      39.630  36.538 -10.597  1.00 84.56      C1
ATOM  3132 CH2 TRP  459      39.562  37.904 -10.852  1.00 84.83      C1
ATOM  3133 C   TRP  459      42.009  35.013  -6.827  1.00 77.31      C1
ATOM  3134 O   TRP  459      41.202  34.344  -7.376  1.00 76.18      C1
ATOM  3135 N   ALA  460      41.557  35.969  -6.020  1.00 76.81      C1
ATOM  3136 H   ALA  460      42.187  36.640  -5.689  1.00  0.00      C1
ATOM  3137 CA  ALA  460      40.158  36.044  -5.613  1.00 76.44      C1
ATOM  3138 CB  ALA  460      40.072  36.724  -4.241  1.00 75.51      C1
ATOM  3139 C   ALA  460      39.678  34.658  -5.538  1.00 76.29      C1
ATOM  3140 O   ALA  460      39.449  37.976  -6.853  1.00 76.98      C1
ATOM  3141 N   PRO  461      38.217  36.147  -7.187  1.00 76.46      C1
ATOM  3142 CD  PRO  461      38.104  34.684  -7.245  1.00 75.88      C1
ATOM  3143 CA  PRO  461      37.242  36.793  -8.068  1.00 75.46      C1
ATOM  3144 CB  PRO  461      36.605  35.605  -8.755  1.00 75.71      C1
ATOM  3145 CG  PRO  461      36.703  34.458  -7.767  1.00 75.60      C1
ATOM  3146 C   PRO  461      36.271  37.803  -7.545  1.00 75.71      C1
ATOM  3147 O   PRO  461      35.677  37.594  -6.440  1.00 73.66      C1
ATOM  3148 N   LEU  462      35.996  38.767  -8.449  1.00 77.19      C1
ATOM  3149 H   LEU  462      36.516  38.723  -9.277  1.00  0.00      C1
ATOM  3150 CA  LEU  462      35.069  39.891  -8.275  1.00 76.87      C1
ATOM  3151 CB  LEU  462      35.674  40.984  -7.360  1.00 78.32      C1
ATOM  3152 CG  LEU  462      34.786  41.959  -6.558  1.00 78.09      C1
ATOM  3153 CD1 LEU  462      34.051  42.987  -7.406  1.00 78.42      C1
ATOM  3154 CD2 LEU  462      33.767  41.092  -5.828  1.00 78.62      C1
ATOM  3155 C   LEU  462      34.701  40.565  -9.611  1.00 80.64      C1
ATOM  3156 OT1 LEU  462      33.507  40.842  -9.808  1.00 81.74      C1
ATOM  3157 OT2 LEU  462      35.606  40.847 -10.417  1.00 81.63      C2
ATOM  3158 CB  LEU  472      22.074  42.654  -1.446  1.00 66.24      C2
ATOM  3159 CG  LEU  472      22.278  44.145  -1.189  1.00 59.68      C2
ATOM  3160 CD1 LEU  472      23.496  44.345  -0.328  1.00 59.16      C2
```

FIGURE 5

```
ATOM  3161 CD2 LEU  472     22.501  -4.883 -2.486  1.00 56.85      C2
ATOM  3162 C   LEU  472     23.504  40.625 -1.996  1.00 63.91      C2
ATOM  3163 O   LEU  472     23.738  39.874 -2.949  1.00 64.90      C2
ATOM  3164 1HT1 LEU  472    21.563  41.441 -3.595  1.00  0.00      C2
ATOM  3165 1HT2 LEU  472    23.091  41.291 -4.237  1.00  0.00      C2
ATOM  3166 N   LEU  472     22.472  41.930 -3.693  1.00 64.29      C2
ATOM  3167 1HT3 LEU  472    22.358  42.849 -4.160  1.00  0.00      C2
ATOM  3168 CA  LEU  472     23.092  42.037 -2.386  1.00 63.85      C2
ATOM  3169 N   ALA  473     23.652  40.229 -0.733  1.00 63.02      C2
ATOM  3170 H   ALA  473     23.533  40.867  0.002  1.00  0.00      C2
ATOM  3171 CA  ALA  473     24.023  38.881 -0.353  1.00 62.37      C2
ATOM  3172 CB  ALA  473     22.870  37.939 -0.558  1.00 63.65      C2
ATOM  3173 C   ALA  473     25.196  38.354 -1.126  1.00 62.01      C2
ATOM  3174 O   ALA  473     26.301  38.651 -0.715  1.00 63.36      C2
ATOM  3175 N   GLY  474     25.032  37.784 -2.306  1.00 61.43      C2
ATOM  3176 H   GLY  474     24.148  37.818 -2.721  1.00  0.00      C2
ATOM  3177 CA  GLY  474     26.101  37.137 -3.047  1.00 63.80      C2
ATOM  3178 C   GLY  474     27.354  37.950 -3.356  1.00 65.13      C2
ATOM  3179 O   GLY  474     28.482  37.417 -3.257  1.00 66.24      C2
ATOM  3180 N   CYS  475     27.175  39.237 -3.757  1.00 64.88      C2
ATOM  3181 H   CYS  475     26.261  39.550 -3.885  1.00  0.00      C2
ATOM  3182 CA  CYS  475     28.308  40.127 -4.068  1.00 61.84      C2
ATOM  3183 CB  CYS  475     27.925  41.413 -4.806  1.00 63.74      C2
ATOM  3184 SG  CYS  475     29.494  42.075 -5.437  1.00 68.86      C2
ATOM  3185 C   CYS  475     28.965  39.567 -2.795  1.00 57.30      C2
ATOM  3186 O   CYS  475     30.214  40.449 -2.724  1.00 57.14      C2
ATOM  3187 N   LEU  476     28.230  40.983 -1.779  1.00 53.29      C2
ATOM  3188 H   LEU  476     27.264  41.024 -1.885  1.00  0.00      C2
ATOM  3189 CA  LEU  476     28.797  41.556 -0.560  1.00 50.43      C2
ATOM  3190 CB  LEU  476     27.719  41.723  0.523  1.00 45.68      C2
ATOM  3191 CG  LEU  476     27.130  43.165  0.497  1.00 42.80      C2
ATOM  3192 CD1 LEU  476     26.670  43.559  1.896  1.00 36.25      C2
ATOM  3193 CD2 LEU  476     28.180  44.180 -0.057  1.00 40.22      C2
ATOM  3194 C   LEU  476     29.546  40.108  0.042  1.00 50.42      C2
ATOM  3195 O   LEU  476     30.614  40.222  0.646  1.00 50.61      C2
ATOM  3196 N   SER  477     29.053  38.932 -0.270  1.00 50.02      C2
ATOM  3197 H   SER  477     28.196  38.860 -0.729  1.00  0.00      C2
ATOM  3198 CA  SER  477     29.721  37.712  0.125  1.00 51.41      C2
ATOM  3199 CB  SER  477     28.778  36.524 -0.051  1.00 53.45      C2
ATOM  3200 OG  SER  477     27.732  36.616  0.926  1.00 57.65      C2
ATOM  3201 HG  SER  477     27.280  37.462  0.828  1.00  0.00      C2
ATOM  3202 C   SER  477     30.978  37.525 -0.681  1.00 50.75      C2
ATOM  3203 O   SER  477     31.980  37.143 -0.068  1.00 51.41      C2
ATOM  3204 N   GLN  478     31.037  37.788 -1.984  1.00 50.21      C2
ATOM  3205 H   GLN  478     30.222  38.056 -2.457  1.00  0.00      C2
ATOM  3206 CA  GLN  478     32.307  37.697 -2.715  1.00 51.37      C2
ATOM  3207 CB  GLN  478     32.064  37.929 -4.166  1.00 53.65      C2
ATOM  3208 CG  GLN  478     31.983  36.570 -4.788  1.00 57.32      C2
ATOM  3209 CD  GLN  478     31.354  36.649 -6.160  1.00 60.47      C2
ATOM  3210 OE1 GLN  478     31.999  36.504 -7.205  1.00 62.26      C2
ATOM  3211 NE2 GLN  478     30.045  36.878 -6.167  1.00 62.16      C2

ATOM  3212 HE21 GLN  478    29.569  36.972 -5.317  1.00  0.00      C2
ATOM  3213 HE22 GLN  478    29.641  36.928 -7.054  1.00  0.00      C2
ATOM  3214 C   GLN  478     33.398  38.670 -2.249  1.00 50.66      C2
ATOM  3215 O   GLN  478     34.584  38.314 -2.217  1.00 50.13      C2
ATOM  3216 N   LEU  479     33.045  39.909 -1.859  1.00 48.78      C2
ATOM  3217 H   LEU  479     32.131  40.223 -2.039  1.00  0.00      C2
ATOM  3218 CA  LEU  479     34.015  40.800 -1.235  1.00 45.87      C2
ATOM  3219 CB  LEU  479     33.434  42.141 -0.847  1.00 42.03      C2
ATOM  3220 CG  LEU  479     32.853  43.083 -1.818  1.00 40.40      C2
ATOM  3221 CD1 LEU  479     32.596  44.393 -1.078  1.00 40.15      C2
ATOM  3222 CD2 LEU  479     33.779  43.258 -3.000  1.00 48.59      C2
ATOM  3223 C   LEU  479     34.505  40.146  0.056  1.00 42.13      C2
ATOM  3224 O   LEU  479     35.695  39.955  0.262  1.00 40.90      C2
ATOM  3225 N   HIS  480     33.609  39.766  0.950  1.00 39.56      C2
ATOM  3226 H   HIS  480     32.658  39.935  0.763  1.00  0.00      C2
ATOM  3227 CA  HIS  480     33.979  39.108  2.179  1.00 37.81      C2
ATOM  3228 CB  HIS  480     32.742  38.714  2.922  1.00 34.29      C2
ATOM  3229 CG  HIS  480     33.094  38.241  4.309  1.00 33.82      C2
ATOM  3230 CD2 HIS  480     33.123  36.932  4.709  1.00 33.44      C2
ATOM  3231 ND1 HIS  480     33.450  38.995  5.344  1.00 34.27      C2
ATOM  3232 HD1 HIS  480     33.505  39.976  5.362  1.00  0.00      C2
ATOM  3233 CE1 HIS  480     33.706  38.223  6.365  1.00 33.80      C2
ATOM  3234 NE2 HIS  480     33.504  36.986  5.965  1.00 37.12      C2
ATOM  3235 HE2 HIS  480     33.637  36.202  6.544  1.00  0.00      C2
ATOM  3236 C   HIS  480     34.836  37.860  1.961  1.00 39.08      C2
ATOM  3237 O   HIS  480     35.716  37.631  2.791  1.00 40.93      C2
ATOM  3238 N   SER  481     34.615  37.029  0.935  1.00 39.24      C2
ATOM  3239 H   SER  481     33.900  37.241  0.305  1.00  0.00      C2
ATOM  3240 CA  SER  481     35.391  35.818  0.683  1.00 38.17      C2
ATOM  3241 CB  SER  481     34.813  34.943 -0.420  1.00 40.42      C2
ATOM  3242 OG  SER  481     33.454  34.597 -0.137  1.00 47.64      C2
ATOM  3243 HG  SER  481     32.898  35.385 -0.162  1.00  0.00      C2
ATOM  3244 C   SER  481     36.724  36.272  0.211  1.00 36.12      C2
ATOM  3245 O   SER  481     37.692  35.793  0.765  1.00 36.23      C2
ATOM  3246 N   GLY  482     36.786  37.206 -0.744  1.00 34.21      C2
ATOM  3247 H   GLY  482     35.956  37.498 -1.168  1.00  0.00      C2
ATOM  3248 CA  GLY  482     38.028  37.792 -1.266  1.00 36.50      C2
ATOM  3249 C   GLY  482     38.958  38.296 -0.151  1.00 36.14      C2
ATOM  3250 O   GLY  482     40.142  37.936 -0.055  1.00 36.65      C2
ATOM  3251 N   LEU  483     38.381  39.084  0.750  1.00 34.64      C2
ATOM  3252 H   LEU  483     37.445  39.326  0.608  1.00  0.00      C2
ATOM  3253 CA  LEU  483     39.073  39.593  1.900  1.00 32.07      C2
ATOM  3254 CB  LEU  483     38.134  40.442  2.731  1.00 31.17      C2
ATOM  3255 CG  LEU  483     37.535  41.687  2.081  1.00 31.01      C2
ATOM  3256 CD1 LEU  483     36.757  42.411  3.156  1.00 30.82      C2
ATOM  3257 CD2 LEU  483     38.599  42.593  1.489  1.00 29.56      C2
ATOM  3258 C   LEU  483     39.600  38.461  2.745  1.00 32.91      C2
ATOM  3259 O   LEU  483     40.752  38.498  3.199  1.00 31.25      C2
ATOM  3260 N   PHE  484     38.767  37.422  2.925  1.00 34.08      C2
ATOM  3261 H   PHE  484     37.930  37.408  2.471  1.00  0.00      C2
ATOM  3262 CA  PHE  484     39.105  36.298  3.788  1.00 34.60      C2
```

FIGURE 5

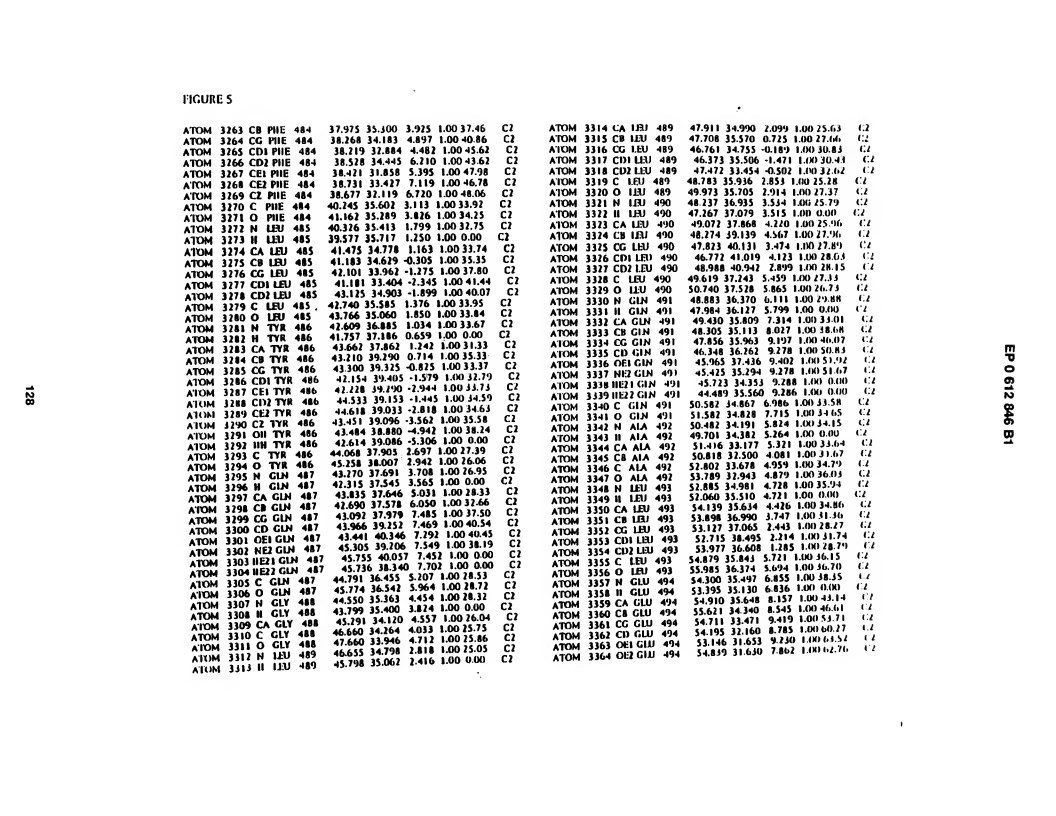


FIGURE 5

```
ATOM  3365 C   GLU  494      55.865  36.825   8.343  1.00 44.32      C2
ATOM  3366 O   GLU  494      57.055  36.678   8.610  1.00 46.91      C2
ATOM  3367 N   GLY  495      55.358  38.046   8.114  1.00 44.32      C2
ATOM  3368 H   GLY  495      54.450  38.112   7.753  1.00  0.00      C2
ATOM  3369 CA  GLY  495      56.104  39.272   8.368  1.00 42.36      C2
ATOM  3370 C   GLY  495      57.015  39.695   7.238  1.00 42.33      C2
ATOM  3371 O   GLY  495      57.397  40.866   7.220  1.00 42.42      C2
ATOM  3372 N   ILE  496      57.310  38.802   6.279  1.00 41.04      C2
ATOM  3373 H   ILE  496      56.927  37.874   6.374  1.00  0.00      C2
ATOM  3374 CA  ILE  496      58.259  38.993   5.192  1.00 41.15      C2
ATOM  3375 CB  ILE  496      57.929  40.216   4.253  1.00 38.60      C2
ATOM  3376 CG2 ILE  496      59.077  40.437   3.248  1.00 37.62      C2
ATOM  3377 CG1 ILE  496      56.662  39.964   3.480  1.00 36.39      C2
ATOM  3378 CD  ILE  496      56.314  41.071   2.470  1.00 35.27      C2
ATOM  3379 C   ILE  496      59.672  39.203   5.749  1.00 42.91      C2
ATOM  3380 O   ILE  496      60.541  38.396   5.448  1.00 44.22      C2
ATOM  3381 N   SER  497      59.998  40.228   6.533  1.00 44.31      C2
ATOM  3382 H   SER  497      59.297  40.852   6.827  1.00  0.00      C2
ATOM  3383 CA  SER  497      61.346  40.501   6.992  1.00 44.86      C2
ATOM  3384 CB  SER  497      62.204  41.254   5.938  1.00 44.13      C2
ATOM  3385 OG  SER  497      62.181  42.673   6.033  1.00 40.74      C2
ATOM  3386 HG  SER  497      62.531  42.964   5.170  1.00  0.00      C2
ATOM  3387 C   SER  497      61.164  41.413   8.185  1.00 45.85      C2
ATOM  3388 O   SER  497      60.132  42.110   8.288  1.00 47.55      C2
ATOM  3389 N   PRO  498      62.164  41.490   9.071  1.00 44.96      C2
ATOM  3390 CD  PRO  498      63.338  40.621   9.126  1.00 42.33      C2
ATOM  3391 CA  PRO  498      62.086  42.327  10.250  1.00 44.88      C2
ATOM  3392 CB  PRO  498      63.431  42.038  10.885  1.00 45.13      C2
ATOM  3393 CG  PRO  498      63.629  40.581  10.603  1.00 42.00      C2
ATOM  3394 C   PRO  498      61.760  43.799   9.983  1.00 45.22      C2
ATOM  3395 O   PRO  498      61.215  44.446  10.869  1.00 45.24      C2
ATOM  3396 N   GLU  499      62.017  44.314   8.777  1.00 46.16      C2
ATOM  3397 H   GLU  499      62.362  43.716   8.081  1.00  0.00      C2
ATOM  3398 CA  GLU  499      61.733  45.699   8.391  1.00 48.06      C2
ATOM  3399 CB  GLU  499      62.498  46.193   7.155  1.00 52.19      C2
ATOM  3400 CG  GLU  499      64.001  46.187   7.100  1.00 57.51      C2
ATOM  3401 CD  GLU  499      64.544  44.737   7.076  1.00 60.61      C2
ATOM  3402 OE1 GLU  499      64.755  44.231   8.162  1.00 62.96      C2
ATOM  3403 OE2 GLU  499      64.739  44.234   5.984  1.00 62.79      C2
ATOM  3404 C   GLU  499      60.269  45.896   7.981  1.00 46.94      C2
ATOM  3405 O   GLU  499      59.600  46.895   8.272  1.00 48.15      C2
ATOM  3406 N   LEU  500      59.806  44.934   7.193  1.00 44.38      C2
ATOM  3407 H   LEU  500      60.351  44.137   7.027  1.00  0.00      C2
ATOM  3408 CA  LEU  500      58.491  44.997   6.651  1.00 41.08      C2
ATOM  3409 CB  LEU  500      58.519  44.197   5.445  1.00 41.37      C2
ATOM  3410 CG  LEU  500      59.303  44.862   4.351  1.00 42.70      C2
ATOM  3411 CD1 LEU  500      59.776  43.828   3.351  1.00 43.98      C2
ATOM  3412 CD2 LEU  500      58.427  45.874   3.671  1.00 45.04      C2
ATOM  3413 C   LEU  500      57.455  44.521   7.628  1.00 40.59      C2
ATOM  3414 O   LEU  500      56.774  44.835   7.463  1.00 40.69      C2
ATOM  3415 N   GLY  501      57.866  43.855   8.685  1.00 39.37      C2
ATOM  3416 H   GLY  501      58.808  43.579   8.730  1.00  0.00      C2
ATOM  3417 CA  GLY  501      56.974  43.386   9.734  1.00 39.59      C2
ATOM  3418 C   GLY  501      55.816  44.324  10.092  1.00 39.66      C2
ATOM  3419 O   GLY  501      54.661  44.034   9.773  1.00 40.66      C2
ATOM  3420 N   PRO  502      55.986  45.462  10.742  1.00 39.90      C2
ATOM  3421 CD  PRO  502      57.227  45.908  11.335  1.00 41.18      C2
ATOM  3422 CA  PRO  502      54.912  46.387  11.045  1.00 38.67      C2
ATOM  3423 CB  PRO  502      55.594  47.494  11.791  1.00 39.23      C2
ATOM  3424 CG  PRO  502      56.989  47.405  11.272  1.00 41.06      C2
ATOM  3425 C   PRO  502      54.158  46.849   9.817  1.00 37.54      C2
ATOM  3426 O   PRO  502      52.966  47.139   9.961  1.00 38.46      C2
ATOM  3427 N   THR  503      54.728  46.887   8.609  1.00 35.13      C2
ATOM  3428 H   THR  503      55.663  46.638   8.449  1.00  0.00      C2
ATOM  3429 CA  THR  503      53.940  47.283   7.462  1.00 35.09      C2
ATOM  3430 CB  THR  503      54.832  47.376   6.245  1.00 34.48      C2
ATOM  3431 OG1 THR  503      56.025  48.018   6.668  1.00 38.23      C2
ATOM  3432 HG1 THR  503      55.857  48.946   6.845  1.00  0.00      C2
ATOM  3433 CG2 THR  503      54.197  48.162   5.126  1.00 35.56      C2
ATOM  3434 C   THR  503      52.836  46.252   7.215  1.00 35.37      C2
ATOM  3435 O   THR  503      51.671  46.552   6.915  1.60 37.11      C2
ATOM  3436 N   LEU  504      53.218  44.996   7.380  1.00 34.02      C2
ATOM  3437 H   LEU  504      54.146  44.799   7.647  1.00  0.00      C2
ATOM  3438 CA  LEU  504      52.301  43.912   7.173  1.00 32.50      C2
ATOM  3439 CB  LEU  504      53.127  42.650   7.002  1.00 34.78      C2
ATOM  3440 CG  LEU  504      53.464  42.256   5.601  1.00 34.07      C2
ATOM  3441 CD1 LEU  504      54.163  40.977   5.667  1.00 37.97      C2
ATOM  3442 CD2 LEU  504      52.254  41.865   4.809  1.00 37.34      C2
ATOM  3443 C   LEU  504      51.324  43.821   8.328  1.00 29.54      C2
ATOM  3444 O   LEU  504      50.141  43.562   8.078  1.00 30.40      C2
ATOM  3445 N   ASP  505      51.736  44.106   9.551  1.00 26.09      C2
ATOM  3446 H   ASP  505      52.689  44.269   9.695  1.00  0.00      C2
ATOM  3447 CA  ASP  505      50.798  44.084  10.643  1.00 27.88      C2
ATOM  3448 CB  ASP  505      51.446  44.345  11.926  1.00 29.86      C2
ATOM  3449 CG  ASP  505      52.500  43.312  12.239  1.00 34.64      C2
ATOM  3450 OD1 ASP  505      52.663  42.298  11.534  1.00 41.04      C2
ATOM  3451 OD2 ASP  505      53.179  43.542  13.224  1.00 37.40      C2
ATOM  3452 C   ASP  505      49.661  45.060  10.568  1.00 28.61      C2
ATOM  3453 O   ASP  505      48.566  44.739  11.039  1.00 30.30      C2
ATOM  3454 N   THR  506      49.894  46.242  10.002  1.00 28.29      C2
ATOM  3455 H   THR  506      50.823  46.493   9.804  1.00  0.00      C2
ATOM  3456 CA  THR  506      48.860  47.225   9.731  1.00 25.74      C2
ATOM  3457 CB  THR  506      49.497  48.556   9.336  1.00 26.14      C2
ATOM  3458 OG1 THR  506      49.944  49.099  10.580  1.00 31.69      C2
ATOM  3459 HG1 THR  506      49.243  49.072  11.346  1.00  0.00      C2
ATOM  3460 CG2 THR  506      48.594  49.517   8.619  1.00 24.46      C2
ATOM  3461 C   THR  506      48.072  46.735   8.615  1.00 24.00      C2
ATOM  3462 O   THR  506      46.817  46.864   8.719  1.00 25.85      C2
ATOM  3463 N   LEU  507      48.554  46.196   7.525  1.00 23.51      C2
ATOM  3464 H   LEU  507      49.527  46.073   7.453  1.00  0.00      C2
ATOM  3465 CA  LEU  507      47.682  45.770   6.434  1.00 21.85      C2
ATOM  3466 CB  LEU  507      48.574  45.408   5.196  1.00 23.11      C2
```

FIGURE 5

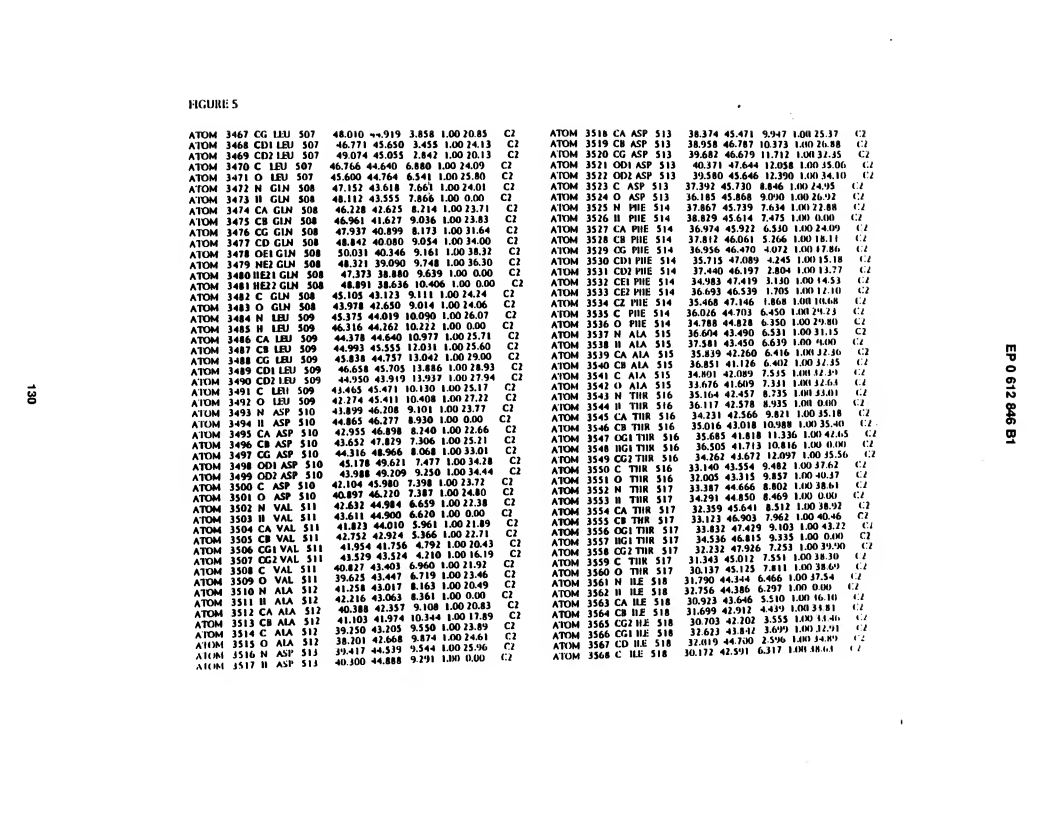

ATOM 3467 CG LEU 507 48.010 44.919 3.858 1.00 20.85 C2
ATOM 3468 CD1 LEU 507 46.771 45.650 3.455 1.00 24.13 C2
ATOM 3469 CD2 LEU 507 49.074 45.055 2.842 1.00 20.13 C2
ATOM 3470 C LEU 507 46.766 44.640 6.880 1.00 24.09 C2
ATOM 3471 O LEU 507 45.600 44.764 6.541 1.00 25.80 C2
ATOM 3472 N GLN 508 47.152 43.618 7.661 1.00 24.01 C2
ATOM 3473 H GLN 508 48.112 43.555 7.866 1.00 0.00 C2
ATOM 3474 CA GLN 508 46.228 42.625 8.214 1.00 23.71 C2
ATOM 3475 CB GLN 508 46.961 41.627 9.036 1.00 23.83 C2
ATOM 3476 CG GLN 508 47.937 40.899 8.173 1.00 31.64 C2
ATOM 3477 CD GLN 508 48.842 40.080 9.054 1.00 34.00 C2
ATOM 3478 OE1 GLN 508 50.031 40.346 9.161 1.00 38.32 C2
ATOM 3479 NE2 GLN 508 48.321 39.090 9.748 1.00 36.30 C2
ATOM 3480 HE21 GLN 508 47.373 38.880 9.639 1.00 0.00 C2
ATOM 3481 HE22 GLN 508 48.891 38.636 10.406 1.00 0.00 C2
ATOM 3482 C GLN 508 45.105 43.123 9.111 1.00 24.24 C2
ATOM 3483 O GLN 508 43.978 42.650 9.014 1.00 24.06 C2
ATOM 3484 N LEU 509 45.375 44.019 10.090 1.00 26.07 C2
ATOM 3485 H LEU 509 46.316 44.262 10.222 1.00 0.00 C2
ATOM 3486 CA LEU 509 44.378 44.640 10.977 1.00 25.71 C2
ATOM 3487 CB LEU 509 44.993 45.555 12.031 1.00 25.60 C2
ATOM 3488 CG LEU 509 45.838 44.757 13.042 1.00 29.00 C2
ATOM 3489 CD1 LEU 509 46.658 45.705 13.886 1.00 28.93 C2
ATOM 3490 CD2 LEU 509 44.950 43.919 13.937 1.00 27.94 C2
ATOM 3491 C LEU 509 43.465 45.471 10.130 1.00 25.17 C2
ATOM 3492 O LEU 509 42.274 45.411 10.408 1.00 27.22 C2
ATOM 3493 N ASP 510 43.899 46.208 9.101 1.00 23.77 C2
ATOM 3494 H ASP 510 44.865 46.277 8.930 1.00 0.00 C2
ATOM 3495 CA ASP 510 42.955 46.898 8.230 1.00 22.66 C2
ATOM 3496 CB ASP 510 43.652 47.829 7.306 1.00 25.21 C2
ATOM 3497 CG ASP 510 44.316 48.966 8.068 1.00 33.01 C2
ATOM 3498 OD1 ASP 510 45.178 49.621 7.477 1.00 34.28 C2
ATOM 3499 OD2 ASP 510 43.988 49.209 9.250 1.00 34.44 C2
ATOM 3500 C ASP 510 42.104 45.980 7.398 1.00 23.72 C2
ATOM 3501 O ASP 510 40.897 46.220 7.387 1.00 24.80 C2
ATOM 3502 N VAL 511 42.632 44.984 6.659 1.00 22.38 C2
ATOM 3503 H VAL 511 43.611 44.900 6.620 1.00 0.00 C2
ATOM 3504 CA VAL 511 41.823 44.010 5.961 1.00 21.89 C2
ATOM 3505 CB VAL 511 42.752 42.924 5.366 1.00 22.71 C2
ATOM 3506 CG1 VAL 511 41.954 41.756 4.792 1.00 20.43 C2
ATOM 3507 CG2 VAL 511 43.529 43.524 4.210 1.00 16.19 C2
ATOM 3508 C VAL 511 40.827 43.403 6.960 1.00 21.92 C2
ATOM 3509 O VAL 511 39.625 43.447 6.719 1.00 23.46 C2
ATOM 3510 N ALA 512 41.258 43.017 8.163 1.00 20.49 C2
ATOM 3511 H ALA 512 42.216 43.063 8.361 1.00 0.00 C2
ATOM 3512 CA ALA 512 40.388 42.357 9.108 1.00 20.83 C2
ATOM 3513 CB ALA 512 41.103 41.974 10.344 1.00 17.89 C2
ATOM 3514 C ALA 512 39.250 43.205 9.550 1.00 23.89 C2
ATOM 3515 O ALA 512 38.201 42.668 9.874 1.00 24.61 C2
ATOM 3516 N ASP 513 39.417 44.539 9.544 1.00 25.96 C2
ATOM 3517 H ASP 513 40.300 44.888 9.291 1.00 0.00 C2
ATOM 3518 CA ASP 513 38.374 45.471 9.947 1.00 25.37 C2
ATOM 3519 CB ASP 513 38.958 46.787 10.373 1.00 26.88 C2
ATOM 3520 CG ASP 513 39.682 46.679 11.712 1.00 31.35 C2
ATOM 3521 OD1 ASP 513 40.371 47.644 12.058 1.00 35.06 C2
ATOM 3522 OD2 ASP 513 39.580 45.646 12.390 1.00 34.10 C2
ATOM 3523 C ASP 513 37.392 45.730 8.846 1.00 24.95 C2
ATOM 3524 O ASP 513 36.185 45.868 9.090 1.00 26.92 C2
ATOM 3525 N PHE 514 37.867 45.739 7.634 1.00 22.88 C2
ATOM 3526 H PHE 514 38.829 45.614 7.475 1.00 0.00 C2
ATOM 3527 CA PHE 514 36.974 45.922 6.530 1.00 24.09 C2
ATOM 3528 CB PHE 514 37.812 46.061 5.266 1.00 18.11 C2
ATOM 3529 CG PHE 514 36.956 46.470 4.072 1.00 17.86 C2
ATOM 3530 CD1 PHE 514 35.715 47.089 4.245 1.00 15.18 C2
ATOM 3531 CD2 PHE 514 37.440 46.197 2.804 1.00 13.77 C2
ATOM 3532 CE1 PHE 514 34.983 47.419 3.140 1.00 14.53 C2
ATOM 3533 CE2 PHE 514 36.693 46.539 1.705 1.00 12.10 C2
ATOM 3534 CZ PHE 514 35.468 47.146 1.868 1.00 10.68 C2
ATOM 3535 C PHE 514 36.026 44.703 6.450 1.00 24.23 C2
ATOM 3536 O PHE 514 34.788 44.828 6.350 1.00 29.80 C2
ATOM 3537 N ALA 515 36.604 43.490 6.531 1.00 31.15 C2
ATOM 3538 H ALA 515 37.581 43.450 6.639 1.00 0.00 C2
ATOM 3539 CA ALA 515 35.839 42.260 6.416 1.00 32.36 C2
ATOM 3540 CB ALA 515 36.851 41.126 6.402 1.00 32.35 C2
ATOM 3541 C ALA 515 34.901 42.089 7.515 1.00 32.89 C2
ATOM 3542 O ALA 515 33.676 41.609 7.331 1.00 32.64 C2
ATOM 3543 N THR 516 35.164 42.457 8.735 1.00 33.01 C2
ATOM 3544 H THR 516 36.117 42.578 8.935 1.00 0.00 C2
ATOM 3545 CA THR 516 34.231 42.566 9.821 1.00 35.18 C2
ATOM 3546 CB THR 516 35.016 43.018 10.988 1.00 35.40 C2
ATOM 3547 OG1 THR 516 35.685 41.818 11.336 1.00 42.65 C2
ATOM 3548 HG1 THR 516 36.505 41.713 10.816 1.00 0.00 C2
ATOM 3549 CG2 THR 516 34.262 43.672 12.097 1.00 35.56 C2
ATOM 3550 C THR 516 33.140 43.554 9.482 1.00 37.62 C2
ATOM 3551 O THR 516 32.005 43.315 9.857 1.00 40.37 C2
ATOM 3552 N THR 517 33.387 44.668 8.802 1.00 38.61 C2
ATOM 3553 H THR 517 34.291 44.850 8.469 1.00 0.00 C2
ATOM 3554 CA THR 517 32.359 45.641 8.512 1.00 38.92 C2
ATOM 3555 CB THR 517 33.123 46.903 7.962 1.00 40.46 C2
ATOM 3556 OG1 THR 517 33.832 47.429 9.103 1.00 43.22 C2
ATOM 3557 HG1 THR 517 34.536 46.815 9.335 1.00 0.00 C2
ATOM 3558 CG2 THR 517 32.232 47.926 7.253 1.00 39.90 C2
ATOM 3559 C THR 517 31.343 45.012 7.551 1.00 38.30 C2
ATOM 3560 O THR 517 30.137 45.125 7.811 1.00 38.69 C2
ATOM 3561 N ILE 518 31.790 44.344 6.466 1.00 37.54 C2
ATOM 3562 H ILE 518 32.756 44.386 6.297 1.00 0.00 C2
ATOM 3563 CA ILE 518 30.923 43.646 5.510 1.00 36.10 C2
ATOM 3564 CB ILE 518 31.699 42.912 4.439 1.00 34.81 C2
ATOM 3565 CG2 ILE 518 30.703 42.202 3.555 1.00 33.46 C2
ATOM 3566 CG1 ILE 518 32.623 43.842 3.699 1.00 32.93 C2
ATOM 3567 CD ILE 518 32.019 44.700 2.596 1.00 34.09 C2
ATOM 3568 C ILE 518 30.172 42.591 6.317 1.00 38.63 C2

FIGURE 5

```
ATOM  3569 O   ILE 518      28.938  4...45   6.205  1.00 39.93      C2
ATOM  3570 N   TRP 519      30.842  41.785   7.179  1.00 38.64      C2
ATOM  3571 H   TRP 519      31.785  41.959   7.361  1.00  0.00      C2
ATOM  3572 CA  TRP 519      30.144  40.784   7.945  1.00 38.15      C2
ATOM  3573 CB  TRP 519      31.124  40.083   8.780  1.00 38.52      C2
ATOM  3574 CG  TRP 519      30.493  38.793   9.255  1.00 42.26      C2
ATOM  3575 CD2 TRP 519      29.880  38.578  10.473  1.00 41.70      C2
ATOM  3576 CE2 TRP 519      29.437  37.278  10.335  1.00 41.69      C2
ATOM  3577 CE3 TRP 519      29.648  39.282  11.629  1.00 42.26      C2
ATOM  3578 CD1 TRP 519      30.448  37.695   8.419  1.00 42.92      C2
ATOM  3579 NE1 TRP 519      29.788  36.793   9.115  1.00 44.19      C2
ATOM  3580 HE1 TRP 519      29.485  35.935   8.741  1.00  0.00      C2
ATOM  3581 CZ2 TRP 519      28.753  36.671  11.360  1.00 41.91      C2
ATOM  3582 CZ3 TRP 519      29.964  38.666  12.652  1.00 41.77      C2
ATOM  3583 CH2 TRP 519      28.522  37.375  12.515  1.00 41.05      C2
ATOM  3584 C   TRP 519      29.027  41.368   8.815  1.00 39.33      C2
ATOM  3585 O   TRP 519      27.888  40.919   8.726  1.00 38.28      C2
ATOM  3586 N   GLN 520      29.264  42.375   9.650  1.00 41.86      C2
ATOM  3587 H   GLN 520      30.180  42.717   9.700  1.00  0.00      C2
ATOM  3588 CA  GLN 520      28.240  43.016  10.464  1.00 44.63      C2
ATOM  3589 CB  GLN 520      28.691  44.198  11.239  1.00 47.03      C2
ATOM  3590 CG  GLN 520      29.602  43.808  12.360  1.00 54.78      C2
ATOM  3591 CD  GLN 520      29.910  45.009  13.243  1.00 60.14      C2
ATOM  3592 OE1 GLN 520      28.988  45.566  13.854  1.00 61.62      C2
ATOM  3593 NE2 GLN 520      31.172  45.456  13.371  1.00 60.46      C2
ATOM  3594 HE21 GLN 520     31.289  46.260  13.910  1.00  0.00      C2
ATOM  3595 HE22 GLN 520     31.895  44.966  12.932  1.00  0.00      C2
ATOM  3596 C   GLN 520      27.144  43.577   9.621  1.00 46.28      C2
ATOM  3597 O   GLN 520      26.001  43.474  10.059  1.00 48.62      C2
ATOM  3598 N   GLN 521      27.362  44.145   8.442  1.00 46.99      C2
ATOM  3599 H   GLN 521      28.272  44.257   8.092  1.00  0.00      C2
ATOM  3600 CA  GLN 521      26.226  44.638   7.716  1.00 49.02      C2
ATOM  3601 CB  GLN 521      26.632  45.553   6.566  1.00 50.06      C2
ATOM  3602 CG  GLN 521      25.456  46.226   5.790  1.00 50.87      C2
ATOM  3603 CD  GLN 521      24.616  47.278   6.534  1.00 51.82      C2
ATOM  3604 OE1 GLN 521      24.864  47.694   7.671  1.00 52.47      C2
ATOM  3605 NE2 GLN 521      23.577  47.776   5.888  1.00 50.36      C2
ATOM  3606 HE21 GLN 521     23.392  47.455   4.987  1.00  0.00      C2
ATOM  3607 HE22 GLN 521     23.044  48.424   6.390  1.00  0.00      C2
ATOM  3608 C   GLN 521      25.454  43.446   7.155  1.00 50.15      C2
ATOM  3609 O   GLN 521      24.214  43.514   7.177  1.00 51.82      C2
ATOM  3610 N   MET 522      26.057  42.348   6.668  1.00 49.18      C2
ATOM  3611 H   MET 522      27.038  42.291   6.688  1.00  0.00      C2
ATOM  3612 CA  MET 522      25.280  41.227   6.171  1.00 48.22      C2
ATOM  3613 CB  MET 522      26.185  40.167   5.607  1.00 46.36      C2
ATOM  3614 CG  MET 522      26.942  40.661   4.412  1.00 44.32      C2
ATOM  3615 SD  MET 522      27.855  39.435   3.476  1.00 48.35      C2
ATOM  3616 CE  MET 522      28.795  38.447   4.565  1.00 42.80      C2
ATOM  3617 C   MET 522      24.453  40.642   7.316  1.00 50.14      C2
ATOM  3618 O   MET 522      23.380  40.124   7.038  1.00 50.60      C2
ATOM  3619 N   GLU 523      24.848  40.722   8.596  1.00 51.91      C2
ATOM  3620 H   GLU 523      25.766  41.031   8.769  1.00  0.00      C2
ATOM  3621 CA  GLU 523      24.027  40.313   9.718  1.00 54.53      C2
ATOM  3622 CB  GLU 523      24.654  40.486  11.081  1.00 54.60      C2
ATOM  3623 CG  GLU 523      25.732  39.525  11.398  1.00 57.05      C2
ATOM  3624 CD  GLU 523      25.386  38.150  10.888  1.00 61.72      C2
ATOM  3625 OE1 GLU 523      24.515  37.487  11.487  1.00 64.66      C2
ATOM  3626 OE2 GLU 523      25.979  37.773   9.872  1.00 63.19      C2
ATOM  3627 C   GLU 523      22.773  41.116   9.836  1.00 58.29      C2
ATOM  3628 O   GLU 523      21.688  40.538   9.850  1.00 59.32      C2
ATOM  3629 N   ALA 524      22.930  42.432   9.992  1.00 61.41      C2
ATOM  3630 H   ALA 524      23.834  42.798  10.024  1.00  0.00      C2
ATOM  3631 CA  ALA 524      21.815  43.360  10.076  1.00 63.58      C2
ATOM  3632 CB  ALA 524      22.382  44.768   9.992  1.00 64.11      C2
ATOM  3633 C   ALA 524      20.818  43.109   8.946  1.00 64.79      C2
ATOM  3634 O   ALA 524      19.655  42.824   9.206  1.00 65.69      C2
ATOM  3635 N   ALA 525      21.251  43.083   7.693  1.00 66.44      C2
ATOM  3636 H   ALA 525      22.196  43.283   7.516  1.00  0.00      C2
ATOM  3637 CA  ALA 525      20.371  42.789   6.574  1.00 68.58      C2
ATOM  3638 CB  ALA 525      21.117  43.044   5.288  1.00 67.42      C2
ATOM  3639 C   ALA 525      19.841  41.356   6.558  1.00 71.11      C2
ATOM  3640 O   ALA 525      19.116  40.946   5.651  1.00 71.65      C2
ATOM  3641 N   GLY 526      20.257  40.510   7.498  1.00 74.20      C2
ATOM  3642 H   GLY 526      21.019  40.780   8.043  1.00  0.00      C2
ATOM  3643 CA  GLY 526      19.728  39.157   7.653  1.00 76.50      C2
ATOM  3644 C   GLY 526      20.430  38.085   6.842  1.00 78.19      C2
ATOM  3645 O   GLY 526      20.174  36.910   7.094  1.00 79.05      C2
ATOM  3646 N   MET 527      21.388  38.433   5.970  1.00 80.25      C2
ATOM  3647 H   MET 527      21.759  39.337   6.075  1.00  0.00      C2
ATOM  3648 CA  MET 527      22.055  37.499   5.063  1.00 81.73      C2
ATOM  3649 CB  MET 527      22.777  38.256   3.928  1.00 82.72      C2
ATOM  3650 CG  MET 527      22.385  39.719   3.720  1.00 83.52      C2
ATOM  3651 SD  MET 527      23.364  40.523   2.436  1.00 87.64      C2
ATOM  3652 CE  MET 527      22.600  42.117   2.462  1.00 84.47      C2
ATOM  3653 C   MET 527      23.078  36.584   5.780  1.00 82.04      C2
ATOM  3654 OT1 MET 527      22.974  35.357   5.624  1.00 83.38      C2
ATOM  3655 OT2 MET 527      23.949  37.104   6.500  1.00 82.90      C2
ATOM  3656 CB  MET 538      47.224  28.531   2.401  1.00 77.43      C3
ATOM  3657 CG  MET 538      47.397  30.041   2.427  1.00 77.15      C3
ATOM  3658 SD  MET 538      46.205  30.708   3.604  1.00 79.03      C3
ATOM  3659 CE  MET 538      44.850  31.067   2.515  1.00 77.20      C3
ATOM  3660 C   MET 538      48.549  27.879   3.086  1.00 75.32      C3
ATOM  3661 O   MET 538      49.130  26.745   0.405  1.00 77.11      C3
ATOM  3662 HT1 MET 538      47.563  26.068   1.449  1.00  0.00      C3
ATOM  3663 HT2 MET 538      46.638  26.204   0.075  1.00  0.00      C3
ATOM  3664 N   MET 538      46.724  26.552   1.050  1.00 77.52      C3
ATOM  3665 HT3 MET 538      45.873  26.401   1.617  1.00  0.00      C3
ATOM  3666 CA  MET 538      47.153  27.940   0.995  1.00 76.57      C3
ATOM  3667 N   PRO 539      49.089  28.870  -0.224  1.00 77.65      C3
ATOM  3668 CD  PRO 539      48.846  29.821  -1.046  1.00 77.26      C3
ATOM  3669 CA  PRO 539      50.526  29.020  -0.349  1.00 78.34      C3
ATOM  3670 CB  PRO 539      50.677  30.465  -1.006  1.00 77.99      C3
```

FIGURE 5

```
ATOM  3671 CG  PRO  539      49.437  30.503  -1.837  1.00 71.52      C3
ATOM  3672 C   PRO  539      51.250  28.931   0.991  1.00 67.83      C3
ATOM  3673 O   PRO  539      50.666  29.294   2.029  1.00 68.05      C3
ATOM  3674 N   ALA  540      52.484  28.417   0.961  1.00 64.48      C3
ATOM  3675 H   ALA  540      52.858  28.098   0.111  1.00  0.00      C3
ATOM  3676 CA  ALA  540      53.389  28.498   2.112  1.00 61.83      C3
ATOM  3677 CB  ALA  540      54.004  27.200   2.619  1.00 63.57      C3
ATOM  3678 C   ALA  540      54.559  29.212   1.496  1.00 58.74      C3
ATOM  3679 O   ALA  540      54.838  29.036   0.301  1.00 58.30      C3
ATOM  3680 N   PHE  541      55.256  30.008   2.292  1.00 55.25      C3
ATOM  3681 H   PHE  541      55.093  30.068   3.257  1.00  0.00      C3
ATOM  3682 CA  PHE  541      56.299  30.814   1.702  1.00 51.38      C3
ATOM  3683 CB  PHE  541      55.964  32.306   1.942  1.00 48.80      C3
ATOM  3684 CG  PHE  541      54.789  32.703   1.058  1.00 45.77      C3
ATOM  3685 CD1 PHE  541      54.992  32.939  -0.279  1.00 44.20      C3
ATOM  3686 CD2 PHE  541      53.507  32.747   1.587  1.00 44.76      C3
ATOM  3687 CE1 PHE  541      53.901  33.207  -1.074  1.00 43.98      C3
ATOM  3688 CE2 PHE  541      52.428  33.018   0.769  1.00 42.86      C3
ATOM  3689 CZ  PHE  541      52.625  33.247  -0.563  1.00 42.52      C3
ATOM  3690 C   PHE  541      57.586  30.364   2.333  1.00 49.80      C3
ATOM  3691 O   PHE  541      58.002  30.807   3.395  1.00 49.55      C3
ATOM  3692 N   ALA  542      58.172  29.442   1.562  1.00 48.21      C3
ATOM  3693 H   ALA  542      57.825  29.298   0.656  1.00  0.00      C3
ATOM  3694 CA  ALA  542      59.326  28.711   1.968  1.00 45.37      C3
ATOM  3695 CB  ALA  542      59.700  27.749   0.898  1.00 45.21      C3
ATOM  3696 C   ALA  543      60.510  29.567   2.266  1.00 44.87      C3
ATOM  3697 O   ALA  542      61.001  29.504   3.374  1.00 46.49      C3
ATOM  3698 N   SER  543      61.013  30.408   1.395  1.00 42.63      C3
ATOM  3699 H   SER  543      60.477  30.685   0.630  1.00  0.00      C3
ATOM  3700 CA  SER  543      62.253  31.108   1.708  1.00 40.31      C3
ATOM  3701 CB  SER  543      63.170  30.861   0.587  1.00 37.74      C3
ATOM  3702 OG  SER  543      62.391  31.181  -0.554  1.00 35.74      C3
ATOM  3703 HG  SER  543      61.824  30.423  -0.751  1.00  0.00      C3
ATOM  3704 C   SER  543      62.087  32.613   1.896  1.00 40.80      C3
ATOM  3705 O   SER  543      61.016  33.115   1.536  1.00 42.63      C3
ATOM  3706 N   ALA  544      63.120  33.383   2.310  1.00 38.84      C3
ATOM  3707 H   ALA  544      63.929  32.951   2.650  1.00  0.00      C3
ATOM  3708 CA  ALA  544      63.035  34.836   2.345  1.00 37.31      C3
ATOM  3709 CB  ALA  544      64.340  35.450   2.808  1.00 35.74      C3
ATOM  3710 C   ALA  544      62.723  35.372   0.947  1.00 37.06      C3
ATOM  3711 O   ALA  544      61.829  36.220   0.820  1.00 38.23      C3
ATOM  3712 N   PHE  545      63.357  34.881  -0.130  1.00 35.72      C3
ATOM  3713 H   PHE  545      64.131  34.298  -0.010  1.00  0.00      C3
ATOM  3714 CA  PHE  545      62.992  35.268  -1.484  1.00 33.66      C3
ATOM  3715 CB  PHE  545      63.738  34.534  -2.593  1.00 29.71      C3
ATOM  3716 CG  PHE  545      63.140  34.742  -3.990  1.00 29.62      C3
ATOM  3717 CD1 PHE  545      62.317  33.788  -4.557  1.00 29.80      C3
ATOM  3718 CD2 PHE  545      63.371  35.915  -4.689  1.00 31.90      C3
ATOM  3719 CE1 PHE  545      61.723  33.984  -5.795  1.00 28.61      C3
ATOM  3720 CE2 PHE  545      62.777  36.113  -5.928  1.00 31.00      C3
ATOM  3721 CZ  PHE  545      61.955  35.150  -6.480  1.00 31.01      C3
ATOM  3722 C   PHE  545      61.543  34.900  -1.667  1.00 34.81      C3
ATOM  3723 O   PHE  545      60.901  35.660  -2.389  1.00 36.88      C3
ATOM  3724 N   GLN  546      60.912  33.847  -1.135  1.00 34.77      C3
ATOM  3725 H   GLN  546      61.396  33.223  -0.558  1.00  0.00      C3
ATOM  3726 CA  GLN  546      59.490  33.637  -1.433  1.00 33.72      C3
ATOM  3727 CB  GLN  546      59.145  32.232  -1.140  1.00 34.85      C3
ATOM  3728 CG  GLN  546      59.582  31.585  -2.444  1.00 42.45      C3
ATOM  3729 CD  GLN  546      59.374  30.085  -2.473  1.00 46.95      C3
ATOM  3730 OE1 GLN  546      59.287  29.472  -1.399  1.00 48.90      C3
ATOM  3731 NE2 GLN  546      59.339  29.442  -3.644  1.00 47.20      C3
ATOM  3732 HE21 GLN  546      59.476  29.944  -4.472  1.00 10.00      C3
ATOM  3733 HE22 GLN  546      59.154  28.481  -3.609  1.00  0.00      C3
ATOM  3734 C   GLN  546      58.504  34.541  -0.729  1.00 31.62      C3
ATOM  3735 O   GLN  546      57.429  34.850  -1.233  1.00 29.88      C3
ATOM  3736 N   ARG  547      58.907  34.929   0.465  1.00 11.09      C3
ATOM  3737 H   ARG  547      59.750  34.566   0.811  1.00  0.00      C3
ATOM  3738 CA  ARG  547      58.160  35.830   1.282  1.00 31.45      C3
ATOM  3739 CB  ARG  547      58.813  35.874   2.601  1.00 31.74      C3
ATOM  3740 CG  ARG  547      57.906  35.224   3.623  1.00 37.02      C3
ATOM  3741 CD  ARG  547      58.344  33.858   4.076  1.00 40.56      C3
ATOM  3742 NE  ARG  547      59.743  34.058   4.345  1.00 47.90      C3
ATOM  3743 HE  ARG  547      60.389  33.924   3.620  1.00  0.00      C3
ATOM  3744 CZ  ARG  547      60.190  34.394   5.543  1.00 49.48      C3
ATOM  3745 NH1 ARG  547      59.361  34.522   6.593  1.00 51.97      C3
ATOM  3746 HH11 ARG  547      58.380  34.356   6.488  1.00  0.00      C3
ATOM  3747 HH12 ARG  547      59.731  34.763   7.491  1.00  0.00      C3
ATOM  3748 NH2 ARG  547      61.464  34.775   5.616  1.00 48.53      C3
ATOM  3749 HH21 ARG  547      62.025  34.803   4.788  1.00  0.00      C3
ATOM  3750 HH22 ARG  547      61.854  35.034   6.501  1.00  0.00      C3
ATOM  3751 C   ARG  547      56.167  37.181   0.590  1.00 32.26      C3
ATOM  3752 O   ARG  547      57.084  37.694   0.317  1.00 34.25      C3
ATOM  3753 N   ARG  548      55.348  37.717   0.205  1.00 31.54      C3
ATOM  3754 H   ARG  548      60.148  37.203   0.444  1.00  0.00      C3
ATOM  3755 CA  ARG  548      54.529  38.980  -0.555  1.00 30.01      C3
ATOM  3756 CB  ARG  548      60.995  39.213  -0.949  1.00 25.42      C3
ATOM  3757 CG  ARG  548      61.820  39.361   0.294  1.00 26.11      C3
ATOM  3758 CD  ARG  548      63.280  39.158  -0.054  1.00 29.34      C3
ATOM  3759 NE  ARG  548      64.044  39.162   1.189  1.00 32.30      C3
ATOM  3760 HE  ARG  548      63.572  38.883   1.995  1.00  0.00      C3
ATOM  3761 CZ  ARG  548      65.344  39.518   1.325  1.00 32.66      C3
ATOM  3762 NH1 ARG  548      66.159  39.923   0.335  1.00 33.98      C3
ATOM  3763 HH11 ARG  548      67.107  40.170   0.533  1.00 10.00      C3
ATOM  3764 HH12 ARG  548      65.812  39.981  -0.600  1.00  0.00      C3
ATOM  3765 NH2 ARG  548      65.837  39.528   2.549  1.00 32.03      C3
ATOM  3766 HH21 ARG  548      66.788  39.783   2.708  1.00  0.00      C3
ATOM  3767 HH22 ARG  548      65.250  39.275   3.321  1.00  0.00      C3
ATOM  3768 C   ARG  548      58.713  38.997  -1.832  1.00 29.81      C3
ATOM  3769 O   ARG  548      57.778  39.790  -1.968  1.00 33.03      C3
ATOM  3770 N   ALA  549      58.979  38.102  -2.761  1.00 27.87      C3
ATOM  3771 H   ALA  549      59.684  37.436  -2.601  1.00  0.00      C3
ATOM  3772 CA  ALA  549      56.227  38.045  -3.984  1.00 27.18      C3
```

FIGURE 5

```
ATOM  3773 CB  ALA  549      58.797  36.934  -4.857  1.00 28.72      C3
ATOM  3774 C   ALA  549      56.748  37.810  -3.770  1.00 25.91      C3
ATOM  3775 O   ALA  549      55.896  38.337  -4.468  1.00 26.03      C3
ATOM  3776 N   GLY  550      56.421  37.074  -2.748  1.00 26.53      C3
ATOM  3777 H   GLY  550      57.103  36.657  -2.185  1.00  0.00      C3
ATOM  3778 CA  GLY  550      55.055  36.805  -2.457  1.00 26.08      C3
ATOM  3779 C   GLY  550      54.410  38.098  -2.075  1.00 26.94      C3
ATOM  3780 O   GLY  550      53.339  38.380  -2.608  1.00 26.59      C3
ATOM  3781 N   GLY  551      55.073  38.917  -1.234  1.00 27.78      C3
ATOM  3782 H   GLY  551      55.958  38.642  -0.925  1.00  0.00      C3
ATOM  3783 CA  GLY  551      54.540  40.212  -0.779  1.00 26.51      C3
ATOM  3784 C   GLY  553      54.302  41.113  -1.994  1.00 26.82      C3
ATOM  3785 O   GLY  551      53.313  41.852  -2.065  1.00 27.82      C3
ATOM  3786 N   VAL  552      55.154  41.013  -3.012  1.00 25.81      C3
ATOM  3787 H   VAL  552      55.916  40.396  -2.954  1.00  0.00      C3
ATOM  3788 CA  VAL  552      54.952  41.843  -4.176  1.00 28.39      C3
ATOM  3789 CB  VAL  552.     56.178  41.743  -5.190  1.00 26.20      C3
ATOM  3790 CG1 VAL  552      55.917  42.391  -6.541  1.00 26.53      C3
ATOM  3791 CG2 VAL  552      57.327  42.546  -4.594  1.00 26.44      C3
ATOM  3792 C   VAL  552      53.650  41.406  -4.820  1.00 29.05      C3
ATOM  3793 O   VAL  552      52.744  42.251  -4.888  1.00 31.68      C3
ATOM  3794 N   LEU  553      53.455  40.120  -5.176  1.00 27.20      C3
ATOM  3795 H   LEU  553      54.122  39.447  -4.908  1.00  0.00      C3
ATOM  3796 CA  LEU  553      52.266  39.705  -5.915  1.00 23.80      C3
ATOM  3797 CB  LEU  553      52.357  38.262  -6.363  1.00 24.86      C3
ATOM  3798 CG  LEU  553      53.432  37.955  -7.357  1.00 23.06      C3
ATOM  3799 CD1 LEU  553      54.073  36.623  -7.092  1.00 24.31      C3
ATOM  3800 CD2 LEU  553      52.794  38.061  -8.703  1.00 21.87      C3
ATOM  3801 C   LEU  553      51.012  39.825  -5.114  1.00 23.72      C3
ATOM  3802 O   LEU  553      49.982  40.138  -5.712  1.00 24.63      C3
ATOM  3803 N   VAL  554      50.962  39.580  -3.803  1.00 24.37      C3
ATOM  3804 H   VAL  554      51.774  39.350  -3.295  1.00  0.00      C3
ATOM  3805 CA  VAL  554      49.660  39.691  -3.180  1.00 26.36      C3
ATOM  3806 CB  VAL  554      49.472  38.751  -1.802  1.00 26.55      C3
ATOM  3807 CG1 VAL  554      50.696  37.933  -1.418  1.00 23.95      C3
ATOM  3808 CG2 VAL  554      48.953  39.614  -0.682  1.00 25.58      C3
ATOM  3809 C   VAL  554      49.322  41.175  -2.960  1.00 27.53      C3
ATOM  3810 O   VAL  554      48.142  41.502  -3.192  1.00 27.44      C3
ATOM  3811 N   ALA  555      50.277  42.106  -2.716  1.00 28.04      C3
ATOM  3812 H   ALA  555      51.221  41.831  -2.658  1.00  0.00      C3
ATOM  3813 CA  ALA  555      49.956  43.539  -2.509  1.00 28.57      C3
ATOM  3814 CB  ALA  555      51.161  44.427  -2.217  1.00 28.07      C3
ATOM  3815 C   ALA  555      49.402  44.055  -3.803  1.00 28.12      C3
ATOM  3816 O   ALA  555      48.425  44.803  -3.847  1.00 30.12      C3
ATOM  3817 N   SER  556      49.985  43.521  -4.839  1.00 26.44      C3
ATOM  3818 H   SER  556      50.781  42.956  -4.710  1.00  0.00      C3
ATOM  3819 CA  SER  556      49.548  43.810  -6.152  1.00 30.09      C3
ATOM  3820 CB  SER  556      50.684  43.277  -6.965  1.00 31.42      C3
ATOM  3821 OG  SER  556      50.442  43.338  -8.344  1.00 37.88      C3
ATOM  3822 HG  SER  556      49.966  44.144  -8.576  1.00  0.00      C3
ATOM  3823 C   SER  556      48.143  43.243  -6.454  1.00 32.78      C3

ATOM  3824 O   SER  556      47.287  43.961  -7.003  1.00 34.56      C3
ATOM  3825 N   HIS  557      47.750  42.019  -6.688  1.00 32.78      C3
ATOM  3826 H   HIS  557      48.350  41.453  -5.560  1.00  0.00      C3
ATOM  3827 CA  HIS  557      46.396  41.605  -6.401  1.00 33.64      C3
ATOM  3828 CB  HIS  557      46.203  40.142  -6.242  1.00 37.88      C3
ATOM  3829 CG  HIS  557      46.986  39.518  -7.348  1.00 42.44      C3
ATOM  3830 CD2 HIS  557      46.694  39.665  -8.675  1.00 43.63      C3
ATOM  3831 ND1 HIS  557      48.108  38.837  -7.299  1.00 45.23      C3
ATOM  3832 HD1 HIS  557      48.641  38.764  -6.385  1.00  0.00      C3
ATOM  3833 CE1 HIS  557      48.524  38.569  -8.414  1.00 46.56      C3
ATOM  3834 NE2 HIS  557      47.676  39.066  -9.283  1.00 45.62      C3
ATOM  3835 HE2 HIS  557      47.793  39.018 -10.257  1.00  0.00      C3
ATOM  3836 C   HIS  557      45.383  42.249  -5.520  1.00 32.94      C3
ATOM  3837 O   HIS  557      44.256  42.444  -5.934  1.00 33.08      C3
ATOM  3838 N   LEU  558      45.744  42.534  -4.280  1.00 33.05      C3
ATOM  3839 H   LEU  558      46.657  42.356  -3.986  1.00  0.00      C3
ATOM  3840 CA  LEU  558      44.817  43.125  -3.348  1.00 31.91      C3
ATOM  3841 CB  LEU  558      45.420  43.107  -1.965  1.00 29.25      C3
ATOM  3842 CG  LEU  558      44.605  43.615  -0.818  1.00 26.02      C3
ATOM  3843 CD1 LEU  558      43.279  42.883  -0.742  1.00 25.00      C3
ATOM  3844 CD2 LEU  558      45.396  43.571   0.408  1.00 27.86      C3
ATOM  3845 C   LEU  558      44.527  44.521  -3.783  1.00 32.47      C3
ATOM  3846 O   LEU  558      43.402  44.944  -3.596  1.00 33.97      C3
ATOM  3847 N   GLN  559      45.482  45.231  -4.370  1.00 34.46      C3
ATOM  3848 H   GLN  559      46.386  44.855  -4.406  1.00  0.00      C3
ATOM  3849 CA  GLN  559      45.255  46.569  -4.912  1.00 36.75      C3
ATOM  3850 CB  GLN  559      46.598  47.067  -5.470  1.00 39.63      C3
ATOM  3851 CG  GLN  559      46.707  48.543  -5.875  1.00 42.00      C3
ATOM  3852 CD  GLN  559      46.530  49.618  -4.793  1.00 41.53      C3
ATOM  3853 OE1 GLN  559      45.961  50.687  -5.057  1.00 41.25      C3
ATOM  3854 NE2 GLN  559      46.951  49.416  -3.561  1.00 37.06      C3
ATOM  3855 HE21 GLN  559      47.271  48.528  -3.311  1.00 0.00      C3
ATOM  3856 HE22 GLN  559      47.001  50.190  -2.967  1.00 0.00      C3
ATOM  3857 C   GLN  559      44.142  46.635  -5.976  1.00 35.22      C3
ATOM  3858 O   GLN  559      43.165  47.404  -5.839  1.00 34.99      C3
ATOM  3859 N   SER  560      44.260  45.817  -7.025  1.00 33.46      C3
ATOM  3860 H   SER  560      45.083  45.292  -7.154  1.00 0.00      C3
ATOM  3861 CA  SER  560      43.222  45.683  -8.049  1.00 32.88      C3
ATOM  3862 CB  SER  560      43.693  44.776  -9.088  1.00 34.05      C3
ATOM  3863 OG  SER  560      45.021  45.174  -9.281  1.00 42.40      C3
ATOM  3864 HG  SER  560      45.042  45.996  -9.783  1.00 0.00      C3
ATOM  3865 C   SER  560      41.885  45.133  -7.559  1.00 32.01      C3
ATOM  3866 O   SER  560      40.791  45.582  -7.970  1.00 32.23      C3
ATOM  3867 N   PHE  561      41.969  44.173  -6.710  1.00 29.50      C3
ATOM  3868 H   PHE  561      42.850  43.767  -6.464  1.00 0.00      C3
ATOM  3869 CA  PHE  561      40.803  43.529  -6.118  1.00 28.17      C3
ATOM  3870 CB  PHE  561      41.237  42.541  -5.040  1.00 26.27      C3
ATOM  3871 CG  PHE  561      40.069  41.966  -4.268  1.00 25.68      C3
ATOM  3872 CD1 PHE  561      39.282  40.999  -4.846  1.00 25.44      C3
ATOM  3873 CD2 PHE  561      39.761  42.482  -3.051  1.00 25.45      C3
ATOM  3874 CE1 PHE  561      38.166  40.551  -4.215  1.00 23.49      C3
```


EP 0 612 846 B1

FIGURE 5

```
ATOM  3875 CE2 PHE  561      38.635  ac.027  -2.421  1.00 26.89      C3
ATOM  3876 CZ  PHE  561      37.853  41.074  -3.008  1.00 24.29      C3
ATOM  3877 C   PHE  561      39.987  44.645  -5.505  1.00 28.81      C3
ATOM  3878 O   PHE  561      38.789  44.697  -5.731  1.00 29.31      C3
ATOM  3879 N   LEU  562      40.672  45.565  -4.797  1.00 28.39      C3
ATOM  3880 H   LEU  562      41.643  45.462  -4.707  1.00  0.00      C3
ATOM  3881 CA  LEU  562      40.033  46.617  -4.057  1.00 26.51      C3
ATOM  3882 CB  LEU  562      40.964  47.203  -3.074  1.00 23.80      C3
ATOM  3883 CG  LEU  562      41.047  46.411  -1.816  1.00 24.85      C3
ATOM  3884 CD1 LEU  562      42.207  46.868  -1.049  1.00 24.07      C3
ATOM  3885 CD2 LEU  562      39.794  46.551  -1.008  1.00 25.13      C3
ATOM  3886 C   LEU  562      39.586  47.669  -4.988  1.00 29.27      C3
ATOM  3887 O   LEU  562      38.580  48.304  -4.681  1.00 29.83      C3
ATOM  3888 N   GLU  563      40.239  47.871  -6.115  1.00 30.88      C3
ATOM  3889 H   GLU  563      41.052  47.368  -6.325  1.00  0.00      C3
ATOM  3890 CA  GLU  563      39.738  48.908  -6.966  1.00 36.88      C3
ATOM  3891 CB  GLU  563      40.660  49.142  -8.137  1.00 40.80      C3
ATOM  3892 CG  GLU  563      41.999  49.628  -7.682  1.00 48.55      C3
ATOM  3893 CD  GLU  563      43.148  49.277  -8.619  1.00 55.42      C3
ATOM  3894 OE1 GLU  563      44.301  49.283  -8.135  1.00 57.39      C3
ATOM  3895 OE2 GLU  563      42.886  48.986  -9.808  1.00 56.44      C3
ATOM  3896 C   GLU  563      38.375  48.469  -7.445  1.00 39.03      C3
ATOM  3897 O   GLU  563      37.388  49.170  -7.270  1.00 39.09      C3
ATOM  3898 N   VAL  564      38.289  47.255  -8.030  1.00 42.30      C3
ATOM  3899 H   VAL  564      39.107  46.714  -8.074  1.00  0.00      C3
ATOM  3900 CA  VAL  564      37.052  46.683  -8.558  1.00 41.84      C3
ATOM  3901 CB  VAL  564      37.333  45.255  -9.041  1.00 42.27      C3
ATOM  3902 CG1 VAL  564      36.055  44.538  -9.435  1.00 41.17      C3
ATOM  3903 CG2 VAL  564      38.283  45.348 -10.241  1.00 42.11      C3
ATOM  3904 C   VAL  564      36.030  46.709  -7.442  1.00 41.68      C3
ATOM  3905 O   VAL  564      34.892  47.015  -7.697  1.00 42.34      C3
ATOM  3906 N   SER  565      36.419  46.501  -6.206  1.00 42.75      C3
ATOM  3907 H   SER  565      37.333  46.173  -6.063  1.00  0.00      C3
ATOM  3908 CA  SER  565      35.567  46.602  -5.064  1.00 44.85      C3
ATOM  3909 CB  SER  565      36.344  46.013  -3.894  1.00 46.54      C3
ATOM  3910 OG  SER  565      35.590  45.714  -2.731  1.00 51.75      C3
ATOM  3911 HG  SER  565      35.060  46.481  -2.491  1.00  0.00      C3
ATOM  3912 C   SER  565      35.167  48.063  -4.871  1.00 45.70      C3
ATOM  3913 O   SER  565      34.038  48.287  -4.446  1.00 46.87      C3
ATOM  3914 N   TYR  566      35.965  49.093  -5.146  1.00 47.59      C3
ATOM  3915 H   TYR  566      36.893  48.908  -5.386  1.00  0.00      C3
ATOM  3916 CA  TYR  566      35.518  50.474  -5.086  1.00 49.68      C3
ATOM  3917 CB  TYR  566      36.765  51.362  -5.164  1.00 56.17      C3
ATOM  3918 CG  TYR  566      36.715  52.622  -6.007  1.00 64.64      C3
ATOM  3919 CD1 TYR  566      37.264  52.538  -7.278  1.00 69.53      C3
ATOM  3920 CE1 TYR  566      37.212  53.613  -8.151  1.00 73.71      C3
ATOM  3921 CD2 TYR  566      36.109  53.797  -5.569  1.00 67.98      C3
ATOM  3922 CE2 TYR  566      36.048  54.888  -6.441  1.00 72.92      C3
ATOM  3923 CZ  TYR  566      36.599  54.787  -7.735  1.00 75.29      C3
ATOM  3924 OH  TYR  566      36.538  55.838  -8.652  1.00 77.42      C3
ATOM  3925 HH  TYR  566      36.905  55.565  -9.494  1.00  0.00      C3

ATOM  3926 C   TYR  566      34.524  50.696  -6.217  1.00 48.48      C3
ATOM  3927 O   TYR  566      33.545  51.376  -5.950  1.00 46.35      C3
ATOM  3928 N   ALA  567      34.679  50.115  -7.417  1.00 49.14      C3
ATOM  3929 H   ALA  567      35.512  49.623  -7.572  1.00  0.00      C3
ATOM  3930 CA  ALA  567      33.670  50.165  -8.490  1.00 52.09      C3
ATOM  3931 CB  ALA  567      34.210  49.574  -9.788  1.00 48.37      C3
ATOM  3932 C   ALA  567      32.315  49.449  -8.238  1.00 55.31      C3
ATOM  3933 O   ALA  567      31.226  50.008  -8.501  1.00 56.87      C3
ATOM  3934 N   VAL  568      32.247  48.211  -7.736  1.00 57.66      C3
ATOM  3935 H   VAL  568      33.083  47.729  -7.564  1.00  0.00      C3
ATOM  3936 CA  VAL  568      30.980  47.573  -7.490  1.00 59.61      C3
ATOM  3937 CB  VAL  568      31.119  46.033  -7.339  1.00 58.96      C3
ATOM  3938 CG1 VAL  568      31.239  45.508  -5.911  1.00 60.27      C3
ATOM  3939 CG2 VAL  568      29.851  45.471  -7.922  1.00 60.44      C3
ATOM  3940 C   VAL  568      30.393  48.177  -6.245  1.00 62.66      C3
ATOM  3941 O   VAL  568      29.174  48.154  -6.180  1.00 64.78      C3
ATOM  3942 N   LEU  569      31.075  48.737  -5.248  1.00 66.15      C3
ATOM  3943 H   LEU  569      32.058  48.719  -5.243  1.00  0.00      C3
ATOM  3944 CA  LEU  569      30.359  49.334  -4.123  1.00 69.85      C3
ATOM  3945 CB  LEU  569      31.285  49.858  -3.023  1.00 69.91      C3
ATOM  3946 CG  LEU  569      32.007  48.887  -2.095  1.00 70.17      C3
ATOM  3947 CD1 LEU  569      32.847  49.687  -1.140  1.00 70.19      C3
ATOM  3948 CD2 LEU  569      31.039  48.054  -1.286  1.00 70.56      C3
ATOM  3949 C   LEU  569      29.567  50.509  -4.667  1.00 72.69      C3
ATOM  3950 O   LEU  569      28.365  50.553  -4.425  1.00 73.80      C3
ATOM  3951 N   ARG  570      30.180  51.391  -5.479  1.00 75.95      C3
ATOM  3952 H   ARG  570      31.153  51.299  -5.580  1.00  0.00      C3
ATOM  3953 CA  ARG  570      29.510  52.498  -6.173  1.00 78.78      C3
ATOM  3954 CB  ARG  570      30.349  53.068  -7.308  1.00 83.47      C3
ATOM  3955 CG  ARG  570      29.658  54.222  -7.997  1.00 84.16      C3
ATOM  3956 CD  ARG  570      29.976  54.744  -9.417  1.00 85.66      C3
ATOM  3957 NE  ARG  570      28.892  55.690  -9.737  1.00 85.67      C3
ATOM  3958 HE  ARG  570      27.971  55.354  -9.727  1.00  0.00      C3
ATOM  3959 CZ  ARG  570      29.051  56.991 -10.026  1.00 85.06      C3
ATOM  3960 NH1 ARG  570      30.240  57.590 -10.082  1.00 84.43      C3
ATOM  3961 HH11 ARG  570      31.069  57.056 -9.908  1.00  0.00      C3
ATOM  3962 HH12 ARG  570      30.295  58.561 -10.314  1.00  0.00      C3
ATOM  3963 NH2 ARG  570      27.958  57.736 -10.154  1.00 84.57      C3
ATOM  3964 HH21 ARG  570      27.059  57.316 -10.030  1.00  0.00      C3
ATOM  3965 HH22 ARG  570      28.042  58.708 -10.375  1.00  0.00      C3
ATOM  3966 C   ARG  570      28.201  52.009  -6.812  1.00 79.92      C3
ATOM  3967 O   ARG  570      27.107  52.565  -6.709  1.00 79.61      C3
ATOM  3968 N   HIS  571      28.362  50.900  -7.511  1.00 81.35      C3
ATOM  3969 H   HIS  571      29.214  50.417  -7.440  1.00  0.00      C3
ATOM  3970 CA  HIS  571      27.247  50.306  -8.197  1.00 82.75      C3
ATOM  3971 CB  HIS  571      27.882  49.274  -9.167  1.00 83.42      C3
ATOM  3972 CG  HIS  571      28.633  50.029 -10.280  1.00 85.08      C3
ATOM  3973 CD2 HIS  571      28.921  49.579 -11.532  1.00 85.81      C3
ATOM  3974 ND1 HIS  571      29.074  51.303 -10.268  1.00 86.25      C3
ATOM  3975 HD1 HIS  571      29.080  51.900  -9.489  1.00  0.00      C3
ATOM  3976 CE1 HIS  571      29.595  51.595 -11.439  1.00 86.31      C3
```

FIGURE 5

```
ATOM  3977 NE2 HIS  571      29.494  50.518 -12.187  1.00 86.28      C3
ATOM  3978 HE2 HIS  571      29.801  50.468 -13.119  1.00  0.00      C3
ATOM  3979 C   HIS  571      26.225  49.759  -7.195  1.00 83.31      C3
ATOM  3980 O   HIS  571      25.075  50.194  -7.301  1.00 84.06      C3
ATOM  3981 N   LEU  572      26.540  48.963  -6.158  1.00 83.11      C3
ATOM  3982 H   LEU  572      27.474  48.824  -5.915  1.00  0.00      C3
ATOM  3983 CA  LEU  572      25.527  48.457  -5.241  1.00 83.71      C3
ATOM  3984 CB  LEU  572      26.085  47.267  -4.454  1.00 83.57      C3
ATOM  3985 CG  LEU  572      25.439  45.884  -4.721  1.00 83.79      C3
ATOM  3986 CD1 LEU  572      25.783  45.286  -6.127  1.00 84.16      C3
ATOM  3987 CD2 LEU  572      25.958  44.866  -3.714  1.00 84.08      C3
ATOM  3988 C   LEU  572      24.997  49.511  -4.261  1.00 84.78      C3
ATOM  3989 O   LEU  572      24.265  49.192  -3.295  1.00 84.85      C3
ATOM  3990 N   ALA  573      25.349  50.796  -4.483  1.00 85.56      C3
ATOM  3991 H   ALA  573      26.020  50.980  -5.174  1.00  0.00      C3
ATOM  3992 CA  ALA  573      24.822  51.925  -3.721  1.00 85.90      C3
ATOM  3993 CB  ALA  573      25.600  53.207  -3.970  1.00 85.79      C3
ATOM  3994 C   ALA  573      23.373  52.245  -4.057  1.00 87.21      C3
ATOM  3995 OT1 ALA  573      22.610  52.413  -3.099  1.00 88.33      C3
ATOM  3996 OT2 ALA  573      23.022  52.309  -5.248  1.00 88.34      C3
ATOM  3997 OH2 H2O  603      26.735  24.280   5.161  1.00 27.42      W
ATOM  3998 H1  H2O  603      27.332  24.335   4.407  1.00  0.00      W
ATOM  3999 H2  H2O  603      26.288  23.435   4.992  1.00  0.00      W
ATOM  4000 OH2 H2O  605      47.880  37.960  12.073  1.00 56.30      W
ATOM  4001 H1  H2O  605      47.789  37.874  13.031  1.00  0.00      W
ATOM  4002 H2  H2O  605      46.980  37.858  11.753  1.00  0.00      W
ATOM  4003 OH2 H2O  607      40.001  49.224   7.214  1.00 40.04      W
ATOM  4004 H1  H2O  607      40.471  48.761   7.909  1.00  0.00      W
ATOM  4005 H2  H2O  607      40.123  48.642   6.457  1.00  0.00      W
ATOM  4006 OH2 H2O  610      59.883  42.530  -9.698  1.00 38.90      W
ATOM  4007 H1  H2O  610      60.512  41.833  -9.477  1.00  0.00      W
ATOM  4008 H2  H2O  610      59.189  42.046 -10.160  1.00  0.00      W
ATOM  4009 OH2 H2O  611      57.178  35.940 -14.270  1.00 34.63      W
ATOM  4010 H1  H2O  611      57.174  36.545 -14.974  1.00  0.00      W
ATOM  4011 H2  H2O  611      57.989  36.211 -13.757  1.00  0.00      W
ATOM  4012 OH2 H2O  612      25.793  27.337  19.130  1.00 29.21      W
ATOM  4013 H1  H2O  612      26.709  27.661  19.145  1.00  0.00      W
ATOM  4014 H2  H2O  612      25.762  26.792  19.929  1.00  0.00      W
ATOM  4015 OH2 H2O  615      29.766  34.284   9.444  1.00 45.03      W
ATOM  4016 H1  H2O  615      30.017  34.618  10.308  1.00  0.00      W
ATOM  4017 H2  H2O  615      29.113  33.592   9.660  1.00  0.00      W
ATOM  4018 OH2 H2O  617      37.316  40.012  10.872  1.00 35.21      W
ATOM  4019 H1  H2O  617      36.600  40.017  11.519  1.00  0.00      W
ATOM  4020 H2  H2O  617      37.944  39.376  11.259  1.00  0.00      W
ATOM  4021 OH2 H2O  619      40.370  52.041  -7.387  1.00 29.62      W
ATOM  4022 H1  H2O  619      40.672  52.724  -6.779  1.00  0.00      W
ATOM  4023 H2  H2O  619      39.505  51.810  -7.052  1.00  0.00      W
ATOM  4024 OH2 H2O  621      27.903  32.440  10.664  1.00 39.99      W
ATOM  4025 H1  H2O  621      27.553  33.207  11.141  1.00  0.00      W
ATOM  4026 H2  H2O  621      27.929  31.808  11.398  1.00  0.00      W
ATOM  4027 OH2 H2O  622      25.057  31.972  13.675  1.00 32.70      W
ATOM  4028 H1  H2O  622      24.393  32.417  14.215  1.00  0.00      W
ATOM  4029 H2  H2O  622      24.469  31.428  13.112  1.00  0.00      W
ATOM  4030 OH2 H2O  623      20.791  28.583  14.218  1.00 50.17      W
ATOM  4031 H1  H2O  623      20.499  28.803  13.325  1.00  0.00      W
ATOM  4032 H2  H2O  623      19.939  28.549  14.688  1.00  0.00      W
ATOM  4033 OH2 H2O  625      22.680  78.881   2.761  1.00 40.48      W
ATOM  4034 H1  H2O  625      21.938  78.856   3.375  1.00  0.00      W
ATOM  4035 H2  H2O  625      22.266  79.246   1.970  1.00  0.00      W
ATOM  4036 OH2 H2O  626      39.689  36.486   9.730  1.00 28.56      W
ATOM  4037 H1  H2O  626      39.090  35.724   9.672  1.00  0.00      W
ATOM  4038 H2  H2O  626      39.627  36.872   8.853  1.00  0.00      W
ATOM  4039 OH2 H2O  627      42.035  78.320   5.697  1.00 46.19      W
ATOM  4040 H1  H2O  627      42.416  77.450   5.832  1.00  0.00      W
ATOM  4041 H2  H2O  627      41.243  78.146   5.181  1.00  0.00      W
ATOM  4042 OH2 H2O  631      47.227  31.440   6.799  1.00 34.47      W
ATOM  4043 H1  H2O  631      47.533  32.209   5.809  1.00  0.00      W
ATOM  4044 H2  H2O  631      47.442  30.713   5.714  1.00  0.00      W
ATOM  4045 OH2 H2O  636      24.043  65.423  -0.336  1.00 73.38      W
ATOM  4046 H1  H2O  636      24.179  65.781  -1.228  1.00  0.00      W
ATOM  4047 H2  H2O  636      23.469  66.096   0.054  1.00  0.00      W
ATOM  4048 OH2 H2O  638      38.984  67.955 -11.226  1.00 29.97      W
ATOM  4049 H1  H2O  638      38.283  67.402 -11.580  1.00  0.00      W
ATOM  4050 H2  H2O  638      39.568  68.046 -11.998  1.00  0.00      W
ATOM  4051 OH2 H2O  639      27.930  66.675  -7.733  1.00 45.40      W
ATOM  4052 H1  H2O  639      28.192  67.028  -6.876  1.00  0.00      W
ATOM  4053 H2  H2O  639      26.979  66.791  -7.705  1.00  0.00      W
ATOM  4054 OH2 H2O  643      50.619  67.802   0.813  1.00 36.55      W
ATOM  4055 H1  H2O  643      51.575  62.904   0.824  1.00  0.00      W
ATOM  4056 H2  H2O  643      50.301  63.665   0.525  1.00  0.00      W
ATOM  4057 OH2 H2O  646      62.897  38.367   3.759  1.00 73.55      W
ATOM  4058 H1  H2O  646      62.414  38.098   2.978  1.00  0.00      W
ATOM  4059 H2  H2O  646      62.244  38.247   4.461  1.00  0.00      W
ATOM  4060 OH2 H2O  650      29.587  68.480  -9.555  1.00 65.67      W
ATOM  4061 H1  H2O  650      28.846  68.630 -10.148  1.00  0.00      W
ATOM  4062 H2  H2O  650      29.180  67.844  -8.936  1.00  0.00      W
ATOM  4063 OH2 H2O  652      51.408  56.331   4.056  1.00 62.90      W
ATOM  4064 H1  H2O  652      50.718  56.353   3.365  1.00  0.00      W
ATOM  4065 H2  H2O  652      51.052  55.671   4.648  1.00  0.00      W
ATOM  4066 OH2 H2O  653      49.404  56.022   2.161  1.00 51.28      W
ATOM  4067 H1  H2O  653      49.442  55.351   1.474  1.00  0.00      W
ATOM  4068 H2  H2O  653      49.323  56.829   1.630  1.00  0.00      W
ATOM  4069 OH2 H2O  654      68.215  42.294  -2.563  1.00 40.77      W
ATOM  4070 H1  H2O  654      68.347  41.745  -1.777  1.00  0.00      W
ATOM  4071 H2  H2O  654      68.189  43.181  -2.190  1.00  0.00      W
ATOM  4072 OH2 H2O  655      66.374  40.425  -2.489  1.00 47.31      W
ATOM  4073 H1  H2O  655      66.936  41.162  -2.766  1.00  0.00      W
ATOM  4074 H2  H2O  655      66.452  39.841  -3.252  1.00  0.00      W
ATOM  4075 OH2 H2O  656      66.927  41.428  -5.011  1.00 44.08      W
ATOM  4076 H1  H2O  656      66.207  42.071  -4.989  1.00  0.00      W
ATOM  4077 H2  H2O  656      67.542  41.824  -4.374  1.00  0.00      W
ATOM  4078 OH2 H2O  657      40.571  57.111   5.740  1.00 66.55      W
```

FIGURE 5

```
ATOM  4079 H1  H2O  657      39.958  ...259   5.613  1.00  0.00      W
ATOM  4080 H2  H2O  657      40.021  57.651   5.014  1.00  0.00      W
ATOM  4081 OH2 H2O  658      48.780  47.580  -3.122  1.00 52.09      W
ATOM  4082 H1  H2O  658      48.811  46.671  -3.438  1.00  0.00      W
ATOM  4083 H2  H2O  658      49.568  47.955  -3.542  1.00  0.00      W
ATOM  4084 OH2 H2O  663      29.095  62.889   1.825  1.00 39.23      W
ATOM  4085 H1  H2O  663      29.380  62.827   2.739  1.00  0.00      W
ATOM  4086 H2  H2O  663      28.377  63.526   1.887  1.00  0.00      W
ATOM  4087 OH2 H2O  664      27.132  25.640   7.430  1.00 50.65      W
ATOM  4088 H1  H2O  664      26.870  24.838   7.876  1.00  0.00      W
ATOM  4089 H2  H2O  664      27.001  25.362   6.496  1.00  0.00      W
ATOM  4090 OH2 H2O  665      23.367  30.554  12.167  1.00 49.69      W
ATOM  4091 H1  H2O  665      24.026  30.006  11.707  1.00  0.00      W
ATOM  4092 H2  H2O  665      22.941  31.016  11.438  1.00  0.00      W
ATOM  4093 OH2 H2O  666      46.015  32.192  10.179  1.00 66.86      W
ATOM  4094 H1  H2O  666      46.060  31.519   9.497  1.00  0.00      W
ATOM  4095 H2  H2O  666      45.411  31.827  10.833  1.00  0.00      W
ATOM  4096 OH2 H2O  667      38.943  37.883  11.978  1.00 47.87      W
ATOM  4097 H1  H2O  667      39.367  37.487  11.188  1.00  0.00      W
ATOM  4098 H2  H2O  667      38.521  37.114  12.362  1.00  0.00      W
ATOM  4099 OH2 H2O  671      33.437  58.101   2.269  1.00 46.65      W
ATOM  4100 H1  H2O  671      33.555  57.162   2.433  1.00  0.00      W
ATOM  4101 H2  H2O  671      33.962  58.514   2.961  1.00  0.00      W
ATOM  4102 OH2 H2O  672      27.551  31.314  20.022  1.00 30.15      W
ATOM  4103 H1  H2O  672      27.929  32.042  20.533  1.00  0.00      W
ATOM  4104 H2  H2O  672      26.845  31.764  19.552  1.00  0.00      W
ATOM  4105 OH2 H2O  673      25.714  36.908  21.385  1.00 36.95      W
ATOM  4106 H1  H2O  673      24.806  37.123  21.637  1.00  0.00      W
ATOM  4107 H2  H2O  673      25.599  36.284  20.654  1.00  0.00      W
ATOM  4108 OH2 H2O  674      38.244  66.897  12.076  1.00 57.36      W
ATOM  4109 H1  H2O  674      37.773  67.536  12.626  1.00  0.00      W
ATOM  4110 H2  H2O  674      38.153  66.104  12.618  1.00  0.00      W
ATOM  4111 OH2 H2O  675      35.762  36.553  -3.986  1.00 58.40      W
ATOM  4112 H1  H2O  675      35.600  37.449  -3.677  1.00  0.00      W
ATOM  4113 H2  H2O  675      35.549  36.642  -4.923  1.00  0.00      W
ATOM  4114 OH2 H2O  676      30.689  32.814  25.675  1.00 59.30      W
ATOM  4115 H1  H2O  676      30.093  33.571  25.680  1.00  0.00      W
ATOM  4116 H2  H2O  676      31.550  33.214  25.540  1.00  0.00      W
END
```


EP 0 612 846 B1

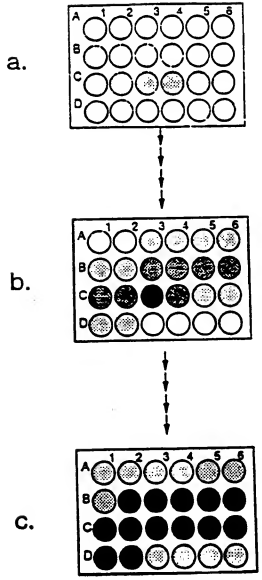


FIGURE 6